Poster session 1: Family planning, fertility, pregnancy and neonatal care

P1:02

ARE LUPUS PATIENTS ON MYCOPHENOLATE COMPLIANT WITH UPDATED PREGNANCY PREVENTION GUIDELINES?

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Objective. Mycophenolate mofetil (MMF) is an immunosuppressant used in the management of systemic lupus erythematosus (SLE). It is a teratogen linked with congenital malformations in around 25% of live births. In 2015 the European Medicines Agency (EMA) released updated recommendations for the avoidance of MMF in pregnancy. For women these included a) two pregnancy tests prior to initiation of therapy 8-10 days apart b) two different forms of contraception during and for 6 weeks after treatment. For men these included a) use of condom during and for 90 days after treatment and b) use of contraception by their female partners for the same period. An audit was conducted.
Design and Method. Patients with SLE who were on MMF were asked to fill a questionnaire based on the guidance. Questions included whether patients were sexually active, their contraceptive use and knowledge of the EMA's advice.
Results. 47 patients on MMF gave responses. All had biopsy proven renal lupus. 7 were male and 40 female. Average treatment duration with MMF was 3 years and median age 37 (range 20-53, SD 9.5). 86% (n=36) were aware that MMF was a teratogen and pregnancy should be avoided.
42 were either male or pre-menopausal women, and of these 64% (n=27) were sexually active. Of these 27, 4 were not using contraception but were aware of the teratogenicity risk whilst 24 were using a single form of contraception only. Despite 70% of the sexually active group (n=19) being aware of the full recommendations regarding contraception none were using 2 forms.
33% (n=8) of the 24 sexually active pre-menopausal women reported having had a pregnancy test before commencing MMF.
Conclusions. Most patients in our cohort were aware of the teratogenicity risk of MMF and were using contraception. However none were using 2 forms of contraception despite the majority being aware of current recommendations. Further only a 1/3 of sexually active women reported having had pre-treatment pregnancy tests. Clinicians managing lupus should be aware of the current MMF guidelines and place specific emphasis on contraceptive advice when counselling sexually active patients.

Key words: mycophenolate, pregnancy, contraception.

P1:03

EFFECT OF PREGNANCY COUNSELLING PRIOR TO CONCEPTION ON THE OUTCOME OF PREGNANCIES IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A PROSPECTIVE STUDY

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Objective. Pregnancies in women with systemic lupus erythematosus (SLE) are associated with increased frequencies of adverse pregnancy outcomes (APOs). Preconception counselling including risk stratification and adjustment of medication is strongly recommended. However, a considerable number of women with SLE do not seek such advice before conception. The goal of this study was to assess the impact of pregnancy counselling prior to conception on the outcome of pregnancies in women with SLE referred to a German lupus pregnancy clinic (2000-2015).
Design and Method. All pregnancies in women with SLE who received an individual pregnancy counselling prior to conception were prospectively followed during pregnancy and postpartum period according to a standard protocol (group A). Outcome of these pregnancies was compared to pregnancies in women with SLE who were already pregnant by the time of their first appointment in our clinic (group B). APOs were defined as fetal loss (spontaneous abortion, stillbirth), severe pregnancy disorders (preeclampsia, HELLP-syndrome), birth before 36 weeks and low birth weight (<2500 g). SLEPDAI was used to gauge disease activity during pregnancy.
Results. A total of 188 pregnancies in 151 women with SLE (median age 31 years) were included [group A = 137; group B = 51]. 67% of all women had been pregnant before, 33% had experienced at least one fetal loss and 9% severe pregnancy disorders. With respect to all pregnancies, a live birth was documented in 172 cases (91.5%) [group A 94.2% vs. group B 86.3%]. A fetal loss occurred in 16 (8.5%) pregnancies [group A 5.8% vs. group B 15.7%]. 23 (12.2%) of all pregnancies were complicated by severe pregnancy disorders [group A 5.8% vs. group B 29.4%] and 28 (14.9%) by preterm birth [group A 7.3% vs. group B 35.3%]. One newborn [Group B] died shortly after extreme preterm birth. After adjusting for maternal age and for higher disease activity in the first trimester (SLEPDAI greater than 4) we observed significantly higher rates of fetal losses (RR=3.4; 95%CI 1.4-8.6), severe pregnancy disorders (RR=5.5; 95%CI 2.5 – 12.1), preterm birth (RR=5.6; 95%CI 2.8 – 11.2) and low birth weight (RR=3.2; 95%CI 1.9 – 5.4) in group B compared to group A.
Conclusions. Our observed overall live birth rate was high and the rates did not significantly differ between the two groups, probably due to an adapted multidisciplinary management during the course of pregnancy. However, pregnancies in women who did not receive counselling prior to conception were associated with significantly higher risks for fetal loss, severe pregnancy disorders, low birth weight and preterm birth. Women with SLE and pregnancy wish should be informed about the beneficial effect of preconception counselling.

Key words: pregnancies in women with SLE, pregancy counselling, adverse pregnancy outcomes

P1:04

RISK FACTORS FOR PREGNANCY MORBIDITY IN PATIENTS WITH ANTIPHOSPHOLIPID ANTIBODIES WITHOUT A DEFINED CLINICAL ANTIPHOSPHOLIPID SYNDROME

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Objective. To define the frequency of pregnancy morbidity in women with positive aPL who do not fit the clinical criteria for APS; to analyze the influence of the serological profile and the load of antibodies associated with these complications, and to determine the efficacy of prophylactic treatment in preventing adverse pregnancy outcome.
Design and Method. We retrospectively analyzed 92 pregnancies in 39 women with a confirmed positive serology for aPL according to Sydney criteria.
Results. Overall, 54% of the 39 pregnant women suffered morbidities: one early pregnancy loss (7), two pregnancies losses (7), fetal death* (1), premature birth* (1), preeclampsia (2) and intrauterine growth restriction (3). After a mean follow-up of 146 ±60,3 months, only 2 patients developed obstetric APS* and none of them developed thrombotic APS. We found no association between the antibody profile and pregnancy morbidities. There was no association between pregnancy complications and the load of antibodies either. Regarding prophylactic treatment, only 8 women received AAS, combined with LWH in 3 of them, we found a non-significant tendency to prevent obstetric events.
When analyzing the 92 pregnancies, we found 28 obstetric events in 26 pregnancies. Mean age for pregnant women was 29.9±5.8 years, gestational age was 38.2±1.8 weeks, birth weight was 3108±482 g and mean Apgar was 8.7±1,1. Regarding treatment influence there was a non significant tendency to prevent obstetric events (OR 0.32, CI 95% 0.87-1.20; p=0.081), that reached statistical significance when analyzing early pregnancy losses (OR 0.12; IC 0.02-0.95; p=0.019). When we restricted the analysis to the 38 pregnancies that were posterior to the positive serology result, we found a significant protective effect of prophylactic treatment (OR=0.15; CI 95% 0.02-0.85; p=0.021), thus conferring a 6.5-fold higher risk of pregnancy complications in the untreated women (IC 95% 1.2-36.33; p=0.032).
Conclusions. a) Pregnancy morbidity rate in women with positive antiphospholipid antibodies was 54% when analyzing the total number of pregnancies, and 32% when analyzing the pregnancies after confirmed positive serology. b) We didn't find a profile of antibodies specifically related with obstetric complications. c) Prophylactic drug therapy is effective in preventing early pregnancy losses and achieving a higher live birth rate.

Key words: antiphospholipid antibodies, pregnancy, morbidity

P1:05

INFERTILITY AND ASSISTED REPRODUCTIVE TECHNOLOGIES: A MULTICENTER STUDY IN PATIENTS WITH SLE AND APS

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Objective. Systemic Lupus Erytematosus (SLE) and Antiphospholipid Syndrome (APS) often affect women in their childbearing ages. Even if their association with fertility problems has not been proved, it is not infrequent that affected patients required Assisted Reproductive Technologies (ART) to obtain a pregnancy.
Design and Method. We described a case series of patients affected by SLE and APS requiring ART in term of pregnancy outcome, fetal-maternal complications and disease flares.
Results. Twenty-two ART attempts in 12 patients (8 SLE and 4 PAPS) have been included. The main features of the patients and of the performed protocols are available in Tab. I.The disease was in remission at the time of procedure in all the cases. A clinical pregnancy has been obtained in 8 cicles (36.4%): 5 by FIVET; 1 by IUI; 2 by ICSI on oocyte donation. Embryo transfer (when applicable): single: 10, double: 3, triple: 1, frozen embryo in 1 case.Prophylaxis during stimulation: 13 (59.1%) LMWH+LDA; 4 (18.2%) LMWH; 2 (9.1%) LDA; 3 (13.6%) without therapy. Prophylaxis during gestation: 3 (37.5%) LMWH+LDA; 1 (12.5%) UH (unfractionated heparin); 3 (37.5%) LDA; 1 (12.5%) without therapy. We recorded: no thrombosis nor ovarian hyperstimulation syndrome and only 1 (4.5%) disease flares (hemolytic anemia in the 2nd trimester). Fetal-Maternal complication was registered in 62.5% of pregnancies (in some cases more than one): 2 IUGR; 2 PROM; 3 oligoanidramnios, 2 maternal thrombocyopenia. Mean gestational age at delivery: 33.3weeks (24-39), mean birth weight 2070g (420-3270), mean birth length: 41.5 cm (28-48).At term delivery in 4 cases (50%), pre-term (mean gestational age at delivery: 28.7 weeks) in 3 cases (37.5%) (1 perinatal death due to extreme prematurity), 1 ongoing.Vaginal delivery in 5 cases (71.4%), cesarean section in 2 (28.6%).

Table I. Primary infertility. no spontaneous pregnancies acheived in the pass; Secondary infertility: onset after one or more spontaneous conceptions; SLE: Systemic Lupus Erythematosus; PAPS: Primary Antiphospholipid Syndrome; success rate: number of clinical pregnancies obtained; aPL: antiphospholipid antibodies.

	12 Patients	
Diagnosis	8 SLE (1+APS); 4 PAPS	
Mean Age, (median), (Range) at the time of procedure	35.1; (34.5); (29-42 years)	
Additional Risk Factors	n: 8 (66.7%): Single: 6 (75%) Multiple: 2 (25%)	
Type of Diagnosed infertility	Primary: 6 (50%), Secondary: 6 (50%). Idiopathic:91.7%	
Type of Protocol performed	Long, with GnRH agonist: 9 (40.9%) Short, with GnRH antagonist: 4 (18.2%) Only gonadotropins: 4 (18.2%) On natural cycle: 3 (13.6%) Clomiphene: 2 (9.1%)	success rate: 11.1% success rate: 50% success rate: 25% success rate: 66.7% success rate: 100%
Thyroid alterations	n: 1 (8.3%)	
Autoantibodies	ENA: 4 (33.3%) aPL: 8 (66.7%): single: 3; double: 3; triple: 2	
Inherited Thrombophilia*	n: 5 (62.5%) (single: 80% double: 20%	

*available in 8 patients.

Conclusions. This is only a preliminary study regarding the application of ART in SLE and PAPS patients. The sample size is obviously insufficient to draw conclusions but our data seems to be reassuring, showing that a careful pharmacological prophylaxis during hormonal stimulation and pregnancy is able to prevent thrombotic complications. Maternal-fetal-complications occurred in more than half of the pregnancies, but the risk of such cases is notoriously increased in gestations induced by ART, while the incidence of maternal disease flare is low.

Key words: ART, SLE and APS, efficacy and safety

P1:06

RISK FACTORS FOR ADVERSE PREGNANCY OUTCOME IN FIRST-LINE TREATED PREGNANCIES IN APL POSITIVE WOMEN ACCORDING TO DIFFERENT TREATMENT STRATEGIES: RESULTS FROM OUR 30 YEARS'EXPERIENCE PREGNANCY CLINIC

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Objective. Antiphospholipid antibodies (aPL) are risk factors for Adverse Pregnancy Outcome (APO). The therapeutic strategy to adopt in aPL patients during pregnancy is still debated. In addition to conventional therapy, some recent evidences suggest a possible role of hydroxychloroquine. We reviewed our approach in first-line treated pregnancies in aPL patients in our 30 years' experience Pregnancy Clinic (1985 -2015) to find out which clinical and serological risk factors have influenced the outcome and the choice of treatment.
Design and Method. We reviewed 120 first-treated pregnancies that were prospectively followed by Rheumatologists/Obstetricians. Patients were classified as Primary Antiphospholipid Syndrome (PAPS) according to revised criteria and as Incomplete PAPS or aPL carriers according to their clinical history or aPL status. Patients with concomitant systemic autoimmune diseases were excluded. aPL profile was defined as the combination of the 3 criteria tests for aPL (Lupus Anticoagulant, anti-cardiolipin, anti-Beta2 Glycoprotein I). APO was defined as at least one of the followings: miscarriage (<10th week), fetal death (>=10th week), severe preterm delivery (<=34th week) with or without preeclampsia (PE), HELLP syndrome or perinatal death.

Table I. #Variables considered for univariate analysis with Fisher's exact test ($p<0.05$).

	Pregnancies with APO (n=16)	Pregnancies without APO (n=104)	P Value
LDA+LMWH (n=68)	**11 (69%)**	**57 (55%)**	
Obstetric PAPS (n=35)	5 (31%)	30 (29%)	
Thrombotic ± Obstetric PAPS (n=12)*	**2 (13%)**	**10 (10%)**	**0.662**
Non-criteria PAPS (n=13)	1 (6%)	12 (12%)	
aPL carriers (n=8)	3 (19%)	5 (5%)	
Single positive (n=34)	4 (25%)	30 (29%)	
Double positive (n=12)	1 (6%)	11 (11%)	
Triple positive (n=22)*	**6 (38%)**	**16 (15%)**	**0.075**
Previous APO (n=52)*	**7 (44%)**	**45 (43%)**	**1.000**
Non-criteria aPL manifestations* (n=9)*	**5 (31%)**	**4 (4%)**	0.002
LDA in single therapy (n=31)	**2 (13%)**	**29 (28%)**	
Obstetric PAPS (n=7)	0 (0%)	7 (7%)	
Thrombotic ± Obstetric PAPS (n=0)*	**0 (0%)**	**0 (0%)**	**1.000**
Non-criteria PAPS (n=11)	0 (0%)	11 (11%)	
aPL carriers (n=13)	2 (13%)	11 (11%)	
Single positive (n=24)	1 (6%)	23 (22%)	
Double positive (n=5)	0 (0%)	5 (5%)	
Triple positive (n=2)*	**1 (6%)**	**1 (1%)**	**0.250**
Previous APO (n=19)*	**0 (0%)**	**19 (18%)**	**0.072**
Non-criteria aPL manifestations* (n=3)*	**0 (0%)**	**3 (3%)**	**1.000**
Corticosteroids + LDA (n=21)	**3 (19%)**	**18 (17%)**	
Obstetric PAPS (n=9)	2 (13%)	7 (7%)	
Thrombotic ± Obstetric PAPS (n=5)*	**0 (0%)**	**5 (5%)**	**1.000**
Non-criteria PAPS (n6=)	1 (6%)	5 (5%)	
aPL carriers (n=1)	0 (0%)	1 (1%)	
Single positive (n=8)	2 (13%)	6 (6%)	
Double positive (n=13)	1 (6%)	12 (12%)	
Triple positive (n=0)*	**0 (0%)**	**0 (0%)**	**1.000**
Previous APO (n=19)*	**3 (19%)**	**16 (15%)**	**0.717**
Non-criteria aPL manifestations* (n=5)*	**1 (6%)**	**4 (4%)**	**0.517**

*Non-criteria aPL manifestations were defined as the presence of at least one of the followings: (livaedo reticularis, thrombocytopenia, headache, hemolytic anemia, cardiac valvulopathy, epilepsy).

Results. The type of therapy was divided in 3 categories: combination therapy with low molecular weight heparin (LMWH) and LDA (68,57%), single therapy with low dose aspirin (LDA) (31,26%) and therapy with corticosteroids plus LDA (21,18%).
We collected 16 APO (13%): 11 (75%) in the category of LMWH+LDA. Ana-

lyzing APO vs. non-APO pregnancies we found no differences in variables that could predict an APO (history of thrombosis, a previous APO or a triple positive aPL profile) in any of the 3 categories (Table I). Moreover, we found an increased rate of non criteria aPL manifestations in APO patients in LMWH+ASA category (31% vs. 4%, *p*:0.002; OR 2.19, 95%CI 2.20-61.6), but not in the other 2 categories of treatment.
Conclusions. Non-criteria aPL manifestations are a risk factor for APO and can determine failure to conventional treatment with LMWH plus LDA during pregnancy in aPL patients regardless of clinical diagnosis, serological profile or obstetric history. These patients may represent a more severe phenotype of disease and may deserve an immunomodulatory treatment to increase the probability of success during pregnancy.

Key words: antiphospholipid antibodies, pregnancy, treatment

P1:07

HYDROXYCLOROQUINE IN PRIMARY APS PREGNANT WOMEN WITH TRIPLE POSITIVITY: EFFECTS ON APL LEVELS AND PREGNANCY OUTCOME

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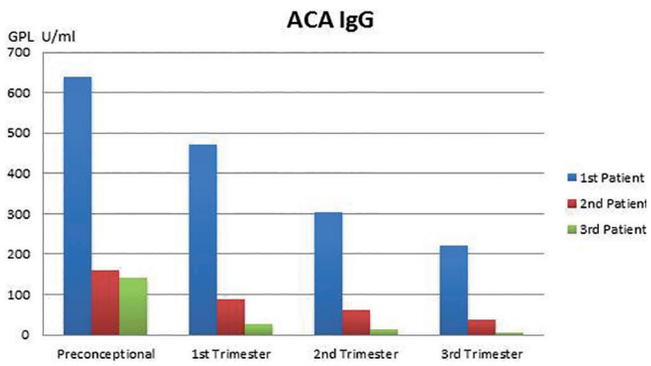
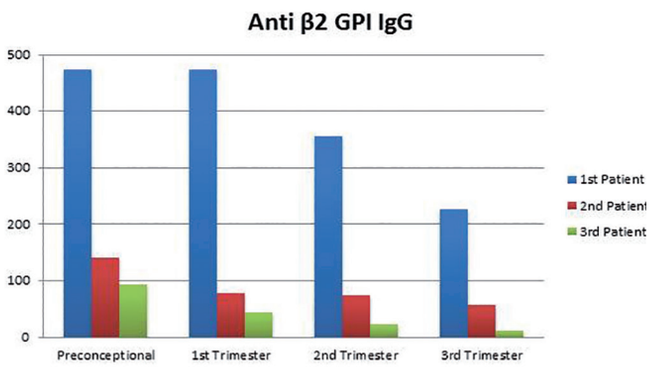
Objective. Prognosis of pregnancies in women with APS has greatly improved: however, some APS patients are unable to give birth to healthy neonates despite the conventional treatment. HCQ seems to be beneficial as additional treatment in pregnant patients with refractory APS. HCQ has been previously demonstrated to be able to reduce aPL titer in not pregnant SLE-patients with associated APS. HCQ works as an anti-inflammatory agent reducing and antagonizing the aPL effect through the inhibition of trophoblast migration, invasion and differentiation. HCQ also inhibits the aPL antibody bindings to syncytiotrophoblasts, restoring annexin A5 expression. Moreover, it is considered an antithrombotic drug, because it is able to reduce the thrombosis recurrence in thrombotic APS. We investigate the effects of HCQ plus conventional treatment in four pregnancies complicated by Primary APS (PAPS) and triple aPL positivity.
Design and Method. Four women with PAPS and triple positivity were eligible for additional treatment with HCQ in order to improve the obstetrical outcome. Levels of ACA (IgG and IgM), anti beta2 GPI (IgG and IgM), LAC and C3 and C4 were tested before pregnancy and repeated at least each trimester. Serial ultrasound examinations and adequate pregnancy management were performed. One patient interrupted HCQ because of adverse effect.
Results. Three live-born babies occurred at week of delivery of 35.6±2.5 with a birth weight of 2176.6±911.9 g, and a birth weight percentile of 27.6±32.3. A good pediatric outcome until 1- 24 months was also reported. In all cases the regimen therapy including HCQ was able to reduce the aPL antibodies levels (Figure 1).
Conclusions. The reduction of the aPL titers could be one of the most important mechanisms that induce pregnancy outcome improvement. We would like to underline the beneficial role of the HCQ in the treatment of refractory obstetrical APS, even if prospective studies need to confirm these preliminary results. In the future it would be hopeful to identify in the preconceptional period those women at highest risk of adverse obstetrical events who require the additional treatment with HCQ in pregnancy.

Key words: hydroxychloroquine, primary APS, pregnancy outcome





P1:08

CONTRACEPTIVE COUNSELING AND USE AMONG PORTUGUESE WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: WHAT IS LACKING?

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Objective. Systemic Lupus Erythematosus (SLE) is a disease that primarily affects women of reproductive age. Disease activity and medication use can complicate pregnancies in SLE, therefore these patients should be counseled and are candidates for highly effective contraceptive methods. We examined contraceptive counseling and use among SLE patients attending a Portuguese Universitary Hospital.
Design and Method. Cross-sectional study in which women aged 15-50 followed in our Rheumatology Centre with a diagnosis of SLE were approached to complete a researcher-administered survey. Premenopausal women <50 years who were sexually active were considered at risk of pregnancy. The statistical analysis was performed using SPSS 23.0 software, and $p<0.05$ was taken to indicate statistical significance. We compared self-reported rates of contraceptive counseling and use, stratified by treatment with teratogenic medications, and by history of thrombosis or antiphospholipid antibodies (aPL), using chi-square tests.
Results. Among 78 women, 49 (62.8%) were at risk for unplanned pregnancy. 51% had received contraceptive counseling; 98% reported consistent contraceptive use: 35% were using hormonal methods, 25% depended solely on barrier methods, intrauterine contraceptives (IUDs) were used by 25% and 15% had had previous tubal ligation. Those who received contraceptive counseling were using more effective contraceptives ($p<0.001$). Women using potentially teratogenic medications or with a history of thrombosis or aPL were no more likely to have received contraceptive counseling or to use more effective contraceptives. History of thrombosis or aPL account for low rates of estrogen-containing contraceptives, however 3 women with aPL were using this type of contraceptives.
Conclusions. In this study, a significant number of patients, including those under potencially teratogenic medications did not receive any contraceptive counseling. These findings suggest the need to improve the education and provision of adequate contraceptive counseling and services to these women.

Key words: contraceptive methods, contraceptive counseling, pregnancy risk

P1:09

PREVALENCE OF DISEASE IN CHILDREN OF MOTHERS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER SYSTEMIC AUTOIMMUNE DISEASES

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Objective. Type IgG auto-antibodies are found in the physiopathology of systemic autoimmune diseases. These immunoglobulins are capable of crossing the placenta, generating in this way damage in the foetus during gestation and the first months of life.
The literature describes that children of mothers with Systemic Lupus Erythematosus (SLE) can present a higher incidence of allergies, skin alterations, intestinal disease, thyroid disease and alterations in psychomotor development.
Analysing whether or not the children of mothers with systemic autoimmune diseases present a higher incidence of disease or alteration of the psychomotor development during infancy in relation to the general population.
Design and Method. A total N of 205 subjects was included among mothers and children (N mothers = 82 and N children = 123). Mothers diagnostic was: 62 = 75,6% SLE, 7 Antiphospholipid Syndrome, 3 Rheumatoid Arthritis, 2 Sjögren Syndrome, 8 other Systemic Autoimmune Diseases. The data were collected in retrospective form through telephone survey made to the mothers followed by the monographic consultation of systemic autoimmune diseases and pregnancy.
Results. In our series 4.87% (N=6) of the children presented the passing of immunoglobulins from the mother to the foetus. The prevalence of asthma was 6.3% (N=20), that of atopic skin was 13% (N=16) and allergy was 13.8% (N=17). The mean of patients that presented backwardness in school or required educational support was 4.1% (N=5).
Conclusions. The incidence of pathologies is similar to the general paediatric population except for a discrete reduction in atopic skin.

Key words: children, prevalence, lupus.

P1:11

NEURODEVELOPMENTAL AFFECTION IN CHILDREN BORN TO MOTHERS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

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Objective. evaluate the neuro-developmental outcome in children born to mothers with SLE or APS and to assess and characterize memory impairment in children's born to mother with systemic lupus erythematosus or APS using children's memory scale and the relation between tetrahydrobiopterin concentration range of children with developmental and neurological disorders.
Design and Method. included women attending rheumatology outpatient clinics at the University of Asyut, SLE patients were eligible if they met the American College of Rheumatology (ACR) criteria for SLE and APL prior to pregnancy, and had at least one live birth following SLE diagnosis. This research approved by the University of Asyut Review Board. Written informed consent obtained from participating mothers; or consent obtained from the offspring for children aged 10–15 years old.
Maternal history Data collected from the mothers during an interview with a maternal fetal medicine investigator, using a structured format that included medical and obstetric history. A detailed history of medication exposures during pregnancy obtained.
Measures of disease activity, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and accrued damage, the Systemic Lupus International Collaborating Clinics Damage Index (SLICCDI), assessed within two weeks.
Offspring history Medical and developmental histories of the offspring of the maternal participants performed, including antenatal, delivery, prenatal and pediatric histories, as child's cognitive, physical or social maturity compared with established age-appropriate norms. Speech or hearing delays, diagnosis of attention-deficit hyperactivity disorder (ADHD), or any special educational needs (eg, occupational or speech therapy, behavioral counseling) recorded. Referrals were categorized according to whether they occurred at any age.
Assessment and characterization of memory impairment using children's memory scale by pediatric neurologists.
Serum Tetrahydrobiopterin (BH4) assays and analyse the BETA2GPI domain were performed by ELISA compared to children born to control healthy subjects of the same age and sex.
Results. Data on 38 mothers and 60 offspring were analysed: ADHD was reported for 15 of 60 (25%) offspring. RECENT MEMORY AFFECTION IN 93% (14/15) Speech delay 40% (6/15). Maternal APS history was significantly associated with increased use special educational need among offsprings, including after adjustment for lupus anticoagulant (LA) positivity (39.4% for delays age >2 years; $p<0.05$).aCLs and anti-BETA2GP1 were not detected to be associated with delays
The presence of LA, but not other antiphospholipid antibodies, was also associated with increased BH4 LEVEL
Conclusions. to improve the knowledge about the prevalence of developmental outcome in children born to mothers with SLE or APS and allow evaluation of relations between The presence of neurodevelopmental abnormalities seems to be more important in these children, and could justify long-term follow-up.
Further studies are necessary to assess the prevalence of neurodevelopmental abnormalities and to analyse the beta-2GPI domain specificity in children with persistent APL, as well as the significance of

Key words: cognitive outcomes, neuropsychological, tetrahydrobiopterin

P1:12

A PREGNANT WOMAN WITH SLE: SEVERE DISEASE FLARE AND SEVERE INFECTION

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Objective. Pregnancy is an immunosuppressive status in which infections could be severe. In immunosuppressed subjects, like patients with autoimmune diseases on corticosteroids therapy, infections must be always suspected when fever rises.
Design and Method. M.C. is a 40 years-old woman with systemic lupus erythematosus (SLE) who became pregnant on January 2015. Her SLE was diagnosed 10 years earlier and characterized by cutaneous involvement, low complement levels, ANA, ENA anti Ro/SSA and dsDNA positivity. The disease was stable before pregnancy and controlled with hydroxycloroquine (400 mg/daily). As soon as she became pregnant she started acetylsalicylic acid 100mg/daily. Since the 7th weeks of gestation the patient presented with a lowering of platelet count that initially remained higher than 100000. At 15th weeks of gestation platelet count fell to 62000; prednisone was started at 10mg/daily and Acetylsalicylic acid was stopped. APL ab were negative. The patient had low C4:12 mg/dl, persistent positivity of dsDNA, while CRP and white blood cells count were normal. Prednisone was increased to 25 mg/daily on the 25th weeks of gestation when the patients presented with a platelet count of 40000. The situation remained stable until the 28th week of gestation when she had abdominal pain with fever and a platelet count of 4000. She was hospitalized and blood cultures resulted positive for Listeria monocytogenes. A cesarean section was done, and the patient was treated with IVIG, pulse steroid (80 mg) and penicillin with a prompt recovery of platelet count that rose to 350000. A baby girl, was born at 28th weeks of gestation + 4 days, with a very low birth weight (1441g) that was adequate for her gestational age. Her APGAR was 8 at 1minute then 5 at 2 minutes, she had a respiratory distress and she remained in neonatal intensive unit care for 3 months. Fortunately the baby clinical course was uneventful.
Nine months after delivery both mother and daughter are doing well: the mother is still taking steroids at 7.5 mg/daily with a platelet count of 150000; the daughter has no sequels.
Results. Listeria monocytogenes is Gram-positive facultative intracellular pathogen often foodborne and found elsewhere. It is an uncommon cause of illness in the general population. However, it has a tropism for placentae and is an important cause of severe infection in neonates, pregnant women, elderly and immunosuppressed patients. Various clinical syndromes have been described such as sepsis, central nervous system infections, endocarditis, gastroenteritis and localized infections; fever is the most common symptom. Maternal listeriosis is a diagnostic challenge and intrauterine infection can lead to severe complications such as amnionitis, preterm labor, spontaneous abortion, stillbirth and neonatal sepsis.
Conclusions. Blood cultures must always be drawn in pregnant women with connective tissue diseases and unexplained fever.

Key words: systemic lupus erythematosus, pregnancy, listeria monocytogenes

P1:13

OUTCOME OF PREGNANCY IN LUPUS NEPHRITIS PATIENTS: DESCRIPTION OF THREE CASES

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Objective. We followed three patients suffering from lupus nephritis (LN) during pregnancy, a great challenge with well described determinants of unfavourable outcome: high disease activity in the last 6 months, proteinuria >0.5g/24h, glomerular filtration rate (GFR) <60 ml/min/1.73m2, hypertension, antiphospholipid syndrome.
Design and Method. Patient 1 was 39 years old, her SLEDAI was 8, proteinuria 1.02 g/24h in a class IV LN. She was on prednisone (PDN) 7.5 mg, azathioprine (AZA) 150 mg, hydroxychloroquine (HCQ) 400 mg/day. Patient 2 was 29 years old, with a SLEDAI of 4 in a class V LN (proteinuria 4.4 g/24h). She was on PDN 5 mg, AZA 100 mg, HCQ 200 mg/day. For them pregnancy was planned after adequate counselling and mycophenolate (MFM) was previously substituted with AZA. Patient 3 had an unplanned pregnancy when she was 20 years old. The SLEDAI was 4 for proteinuria >0.5 g/24h in a class IV LN. She was taking PDN 10 mg/day. No patients were antiphospholipid antibodies positive.
They all underwent monthly multidisciplinary management by rheumatologist, nephrologist and obstetrician.
Results. During pregnancy, all patients had worsening of disease activity. GFR remained >60 ml/min/1.73m2, but their proteinuria rose to 2.8, 5.7 and 3.1 g/24 respectively and patients 2 and 3 had anti-dsDNA antibodies positivity.
Therapy was not modified in patient 1, PDN was increased to 10 mg and AZA to 150 mg daily in patient 2. PDN 25 mg and HCQ 200 mg/day were introduced in patient 3.
They were all treated with methyldopa for hypertension and with prophylactic acetylsalicylic acid.
The deliveries were at 34, 32+5 and 33+5 weeks respectively. Babies were all healthy, with low birth weights, appropriate for gestational ages. After birth, renal disease improved in patient 1 and 2; patient 3 had a LN flare treated with cylophosphamide and rituximab, then with MFM, without remission, also because of the incomplete compliance; hemodialysis was started 10 months later.
Conclusions. Pregnancy in active LN patients can have a good outcome even in presence of poor prognostic features. It should be carefully planned and therapy modified before conception in order to have stability with safe therapies; tight monitoring and multidisciplinary management are mandatory.

Key words: lupus nephritis, pregnancy, multidisciplinary management

P1:14

PREVALENCE OF ABORTIONS AND FETAL ATRIOVENTRICULAR BLOCK IN PATIENTS WITH POSITIVE ANTI-RO AND ANTI-LA ANTIBODIES

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Objective. To characterise a cohort of patients with positive anti-SSA/Ro and/or anti-SSB/La antibodies and to evaluate the prevalence of abortions and neonatal mortality.
Design and Method. Observational descriptive study with 162 patients older than 15 years old with pregnancies history and positive anti-SSA/Ro and/or anti-SSB/La antibodies from February 2011 to July 2015. We consider healthy women with pregnancies history and with comparable characteristics as negative control group.
Results. We included 162 patients with positive anti-SSA/Ro and/or anti-SSB/La antibodies with a mean age of 50.5±14.2 years old. Main diagnoses were systemic lupus erythematosus (n=85), Sjögren syndrome (n=40), rheumatoid arthritis (n=16), systemic sclerosis (n=6), mixed connective tissue disease (n=3) and other diagnosis (n=12). Lupus anticoagulant was positive in 8 cases and 57 patients showed low complement values. 37% of patients had at least one pregnancy, and the 36.7% aborted during pregnancy.
There were no significant differences in the abortion incidence between our cohort of patients and the healthy control group considered.
We observed 4 cases of fetal atrioventricular block, all of them with positive anti-SSA/Ro and/or anti-SSB/La antibodies and only in one case also with positive lupus anticoagulant.
Conclusions. In our series, pregnant women with positive anti-SSA/Ro and/or anti-SSB/La antibodies did not show high prevalence of abortion. However, the positivity of these antibodies was statistically correlated with the presence of fetal atrioventricular block.

Key words: anti-Ro, fetal atrioventricular block, anti-La

P1:15

SEVERE FOETAL GROWTH RESTRICTION DUE TO EXTENSIVE PLACENTAL DAMAGE IN A WOMAN WITH ANTINUCLEAR AND ANTI SSA/RO ANTIBODIES. A CASE REPORT

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Objective. Placental damage has multiple aetiologies and often result unexplained. Autoimmune diseases, despite rare, have a disproportionately high probability of placental dysfunction. Whether isolated antinuclear (ANA) serology should be considered risk factor in the absence of active connective tissue disease (CTD) is still unknown. This case study gives a clue.
Design and Method. A 38-year-old female had her first pregnancy terminated at 22 weeks gestation. She had been treated for acute ANA-positive immune thrombocytopenic purpura (ITP) at the age of 23, but was otherwise remarkably healthy (BMI of 21). Routine blood tests, thyroid function, urine were normal. Platelets remained over $150x10^3$/microL throughout pregnancy. Immunologic tests showed ANA 1:1280 fine speckled on HEP2 cells, and anti SSA/Ro antibodies, confirmed by immunoblot (60 KD). Anti dsDNA, anti-Phospolipids (APL), direct and indirect Coombs tests were negative. Complement C3c and C4 were in the normal range. Echocardiographic screening for foetal atrioventricular heart block gave normal results since the 16th week. At 18 weeks, growth restriction under 5th percentile, and placental flow abnormalities were detected on ultrasound and Doppler velocimetry. A decision was made to terminate the pregnancy at 22 weeks due to growth arrest. The placenta weighed 320 grams; large infarctions covered 80% of its surface. Decidua and villi had features of leukocytoclastic vasculitis, mural thrombosis and fibrin deposition. A massive C3 and moderate IGG and IGA deposition were present on the villi's basal membrane. The fetus had no immune deposits, no cardiac conduction tissue lesions nor major congenital abnormalities. A month later congenital thrombophilic abnormalities were not found at blood tests.
Results. We describe a healthy pregnant woman with typical CTD serology and previous ITP. Severe growth restriction developed due to extensive placental ischemia in the contest of vasculitis and diffuse immune deposition. Risks factors for pregnancy complications in Systemic Lupus Erythematosus are active disease, proteinuria, organ damage, thrombocytopenia, and complement defects. APL serology confers the higher risk of unfavourable outcome. None of these features were present in our patient. Pregnancy is considered rather safe in other CTDs without visceral involvement. A fine balance between inflammation and growth factors favouring invasion, remodelling, angiogenesis, and tolerance enables placentation. We hypothesise that occult immune injuries may interfere with normal placentation by producing tissue and vascular inflammatory and thrombotic phenomena.
Conclusions. The significance of ANA positivity in unexpected placental pathology is a topic of discussion, and universal testing is not recommended. The impact of anti SSa/Ro antibodies on pregnancy outcome remain uncertain. This case indicates that, in a woman with previous immunological events, a high titre ANA and anti SSa/Ro may produce placental lesions in absence of overt systemic disease. This suggests that these pregnancies should be considered at high risk and rigorously monitored with obstetric, medical and immunological follow-up.

Key words: foetal growth restriction, placental pathology, autoantibodies

P1:16

PREGNANCY OUTCOME IN SYSTEMIC LUPUS ERYTHEMATOSUS IN RELATION TO DISEASE ONSET

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Objective. To analyze pregnancy outcome in systemic lupus erythematosus (SLE) in relation to disease onset.
Design and Method. We analyzed twenty-five pregnancies within a 5-year period in a single tertiary medical center. Pregnancies were divided into two groups: group A - patients with SLE diagnosed preconception and group B - patients with SLE onset during the pregnancy or postpartum.
Results. Group A included 20 pregnancies, of which 85% planned and 90% in remission at the time of conception. Antiphospholipid syndrome (APS) and/or hereditary thrombophilia (C+S protein deficiency and homozygote mutations) were present in 75% of patients, requiring anticoagulant and/or antiplatelet prophylaxis. Anti-Ro positivity was present in half of the group; 10 patients had a history of lupus nephritis. Preeclampsia and hypertension were recorded in 20% of patients and fetal complications in 26% (3 still births, 2 premature births, 1 atrial septal defect). Group B included 5 cases: one case diagnosed with preeclampsia and full-blown lupus in the third trimester; the rest diagnosed postpartum. APS and/or hereditary homozygote thrombophilia were associated in 80%; fetal complications were recorded in 80% of cases: 2 premature and 2 still births. Group B was associated with significant worse fetal outcome (26% vs 80%, p=0.03). Other determinants of poor fetal outcome were lack of pregnancy planning (p=0.05) and the association of APS and/or hereditary thrombophilia (p=0.01), but not age, disease duration or a history of lupus nephritis.
Conclusions. SLE is a high risk pregnancy; poor fetal outcome is associated with disease onset during pregnancy or postpartum, lack of pregnancy planning and the presence of associated APS and/or hereditary thrombophilia.

Key words: pregnancy, poor fetal outcome, antiphospholipid syndrome

Poster session 2: Innate immunity, autoantibodies and infections

P2:18

IFN(ALPHA)-MEDIATED DEREGULATION OF MITOCHONDRIAL DNA CLEARANCE PROMOTES THE AUTOREACTIVE PHENOTYPE OF PERIPHERAL BLOOD MONOCYTES IN HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Mitochondrial (mt)DNA – an unmethylated form of DNA of bacterial origin – is a known cytoplasmic danger signal that could trigger anti-DNA immune responses. We sought to explore the role of mtDNA in promoting the immunogenic potential of peripheral blood monocytes in human systemic lupus erythematosus (SLE).
Design and Method. Serum and peripheral blood CD14+ monocytes were isolated from active, newly diagnosed or off-treatment SLE patients (n=35) and age and sex matched healthy donors (n=30). IFN-alpha signalling was induced by treatment with either 10% SLE serum or rec-hIFN-alpha. Autophagy, was assessed by QPCR, immunoblotting and confocal microscopy for Atg5, LC3, P62-SQSTM1 and LAMP-1. Autophagy was induced with rapamycin and its completion was inhibited by hydroxychloroquine. Antigen presenting capacity of monocytes and T cell proliferation after MLRs were assessed by flow cytometry for HLA-DR, CD86 and CFSE, respectively. Autophagolysosomal pH, mtROS production, mt-membrane polarization and mtDNA accumulation were assessed by confocal microscopy and flow cytometry using specific fluorescent dyes (Lysotracker Red-DND99, mitoSOX, JC-1, MitotrackerRed CMXRos and picogreen respectively).
Results. Freshly isolated SLE monocytes and healthy human monocytes exposed to SLE serum or rIFN-alpha exhibited increased autophagosome formation (p<0,005) but defective autophagolysosomal degradation of intracellular components. Lysosomal pH was less acidic and lysosomal enzyme functionality was compromised (evidenced by cathepsin D hypo-activity) both in freshly isolated SLE (p<0,0005) and in healthy monocytes cultured with IFNalpha (p<0,005). Lysosomal alkalinization correlated with increased mtROS production and intracellular ATP decrease, leading to accumulation of damaged, oxidizing mitochondria and increased survival of mtDNA inside cytoplasmic compartments fused with lysosomes. When autolysosomal hypofunctionality was rescued by the addition of rapamycin (autophagy inducer) or mtROS scavenger, IFNalpha-differentiated monocytes displayed reduced antigen presenting capacity (assayed by MLRs with naïve $CD4^+$ T cells) and reduced production of TNF-α, IL6 and IL1beta. Ongoing experiments address the fate of unprocessed mtDNA fragments and the sensor(s) it activates to promote and sustain anti-DNA inflammatory responses in SLE monocytes.
Conclusions. In lupus, IFN-alpha shapes the autophagic flux in peripheral blood monocytes and thus impacts on intracellular oxidation through effects in mitochondrial turnover. Autolysosomal escape of mt DNA in SLE monocytes is sensed and promotes the immunogenicity/immunoreactivity of SLE monocytes that may support and sustain autoimmunity.

Key words: type I interferon, autophagy, mitochondria

P2:19

IN VITRO IFN ALPHA TREATMENT UP-REGULATE BLYS GENE EXPRESSION IN A HUMAN MONOCYTIC AND MACROPHAGE-DERIVED CELL LINE

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Objective. Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by a continuous activation of type I Interferon (IFN) system. High serum levels of IFNα are associated with the severity of the disease. BLyS (B Lymphocyte Stimulator) is a monocyte lineage specific cytokine that promotes B-cell survival, differentiation and proliferation; it is over-expressed in SLE patients. Murine models and *in vitro* experiments on human monocyte primary cells demonstrate that IFNα treatment increases BLyS mRNA and protein expression. Our aim was to confirm, in a human monocytic and macrophage-derived cell line, the up-regulation of BLyS mRNA expression after IFNα treatment.
Design and Method. Human monocyte U937 cells (500.000 cells/mL) and macrophage-derived U937 cells (500.000 cells/mL induced with 50 ng/mL PMA -phorbol 12-myristate 13-acetate- for 72 hours), were treated with 1000 IU/mL IFNα, and cells were harvested to extract total mRNA after 6, 10, 24 and 48 hours; BLyS gene expression was analyzed by RT-qPCR using GAPDH as reference gene. Untreated samples at every time point were considered as controls. Primers were used at a final concentration of 100nM. Statistical analysis was performed by REST-384 version 2 using Pair Wise Fixed Reallocation Randomisation Test.

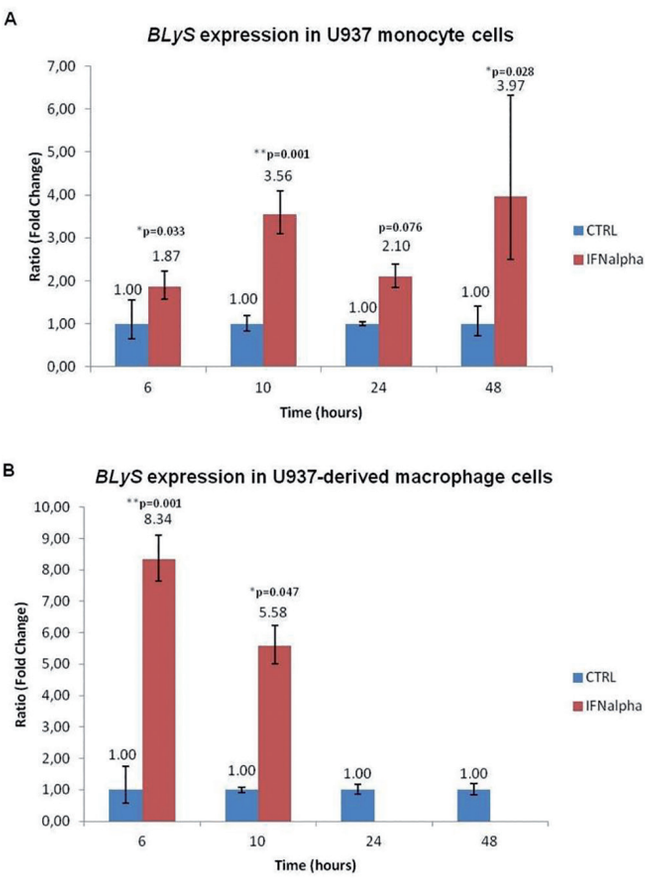

Figure1: *BLyS* mRNA expression in U937 monocyte (**A**) and macrophage-derived cells (**B**) after IFNα (1000 IU/mL) exposure. The ratio of *BLyS* mRNA levels to *GAPDH* mRNA was calculated in unit (Fold Change). The ratios of mRNA levels in untreated cells (CTRL) at each time point are indicated as 1. The error bars represent the standard deviation. *p<0.05; **p<0.001.

Results. Monocyte cells did not show any morphological change during the time of treatment, while macrophage-derived cells showed marked signs of pyknosis after 24 hours treatment with IFNα. U937 monocytes showed a significant up-regulation of BLyS mRNA expression at 6 hours (p=0.033), 10 hours (p=0.001) and 48 hours (p=0.028) (Figure 1A). U937-derived macrophages showed a significant up-regulation at 6 hours (p=0.001) and 10 hours (p=0.047), while at 24 hours and 48 hours RNA extraction was not possible probably due to treatment induced degradation (Figure 1B).
Conclusions. IFNα treatment induces up-regulation of BLyS mRNA within 10 hours, and seems to have a major role in macrophage-derived cells, confirming the role of IFNα in sustaining BLyS-mediated B cell activity in SLE, and suggesting a link between innate and adaptive immunity in this autoimmune disease.

Key.words: interferon alpha, B Lymphocyte stimulator, human monocytic cell line

P2:20

LUPUS SYNDROME INDUCED BY ANTI TNF DOES NOT SEEM TO BE RELATED TO THE APPEARANCE OF ANTIBODIES AGAINST THE MEDICATION (ADAB)

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Objective. Anti TNF therapy can induce auto immunity: production of auto antibodies (ANA, more rarely anti-dsDNA) but also immunogenicity: development anti drug antibodies (ADAb). The relation between the two disorders is not well known although they can occur in the same patients and both can lead to the reappearance of arthralgia.
The goal of the study was to determine if in presence of ADAb, autoimmunity was more frequent and therefore could potentially trigger such antibodies.
Design and Method. Since the beginning of 2013, the measurement of antibodies against anti-TNF (ADAb) has been introduced in our hospital and validated. ADAb were found in 45 out of the 150 patients under anti-TNF therapy.
In 22 patients with ADAb +, anti-nuclear and anti dsDNA antibodies could also be also analyzed at the same time as the ADAb assays. The results were compared with 22 ADAb- patients matched to ADAb+ patients in term of age, gender, type of illness and type of medication.
Results. 11 patients had high level ADAb against infliximab (>200), 4 against adalinumab and 1 against golinumab. Auto antibodies (ANA, dsDNA) induced by anti–TNF were frequent in both ADAb+ and ADAb- patients without significant differences (see table).

	At time of ADAb dosages number of patients		Ever since on anti TNF number of patients	
	ADAb+	ADAb-	ADAb+	ADAb-
Anti nuclear + (>1/320)	8/22	12/22	10/22	13/22
Anti sDNA + (>200Ui)	4/22	1/22	4/22	1/22

Conclusions. Our study suggests that auto immunity is as frequent in absence of ADAb as in presence of such antibodies. The physiopathology of both disorders seems therefore not to be linked.

Key words: autoimmunity, immunogenicity, lupus

P2:21

SIGLEC-1-POSITIVE PLASMACYTOID DENDRITIC CELLS (PDCS) IN HUMAN PERIPHERAL BLOOD: A SEMI-MATURE AND MYELOID-LIKE SUBSET IMBALANCED IN SLE

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Objective. Plasmacytoid dendritic cells (pDCs) are considered a crucial element in SLE pathogenesis due to their potency to produce high levels of IFN-α. This innate immunological function of pDCs is lost by terminal differentiation into a professional antigen-presenting cell, thereby upregulating costimulatory molecules and downregulating innate characteristics, *e.g.* IFN-α expression. Siglec-1 (sialoadhesin, CD169) is an adhesion molecule first characterized on cells of the macrophage-monocyte lineage. Expression of Siglec-1 on monocytes was identified as an IFN-α -regulated marker for active disease in SLE. Siglec-1 is suggested to play a role in the regulation of adaptive immune responses. The impact of Siglec-1 in adaptive immunity together with its nature as IFN-α regulated molecule prompted us to study Siglec-1 in pDCs with focus on SLE pathogenesis.
Design and Method. An 8-color-flowcytometric analysis was performed on whole blood of healthy donors and SLE patients. PDCs were identified by CD3-/CD19-/CD14-/CD123high//BDCA-2+/HLA-DR+ expression and characterized for Siglec-1, CD86 and CD83. *In vitro* stimulation of intracellular IFN-α expression by TLR7 ligand Imiquimod-R837 and TLR9 ligand CpG-A was studied in MACS-sorted pDCs. Surface Siglec-1 induction by recombinant IFN-α and influenza virus vaccine (Begripal 2011/2012, Novartis) was studied in pDCs, too.
Results. We found a small subpopulation of Siglec-1 expressing pDCs in human peripheral blood. Compared to Siglec-1 negative pDCs, Siglec-1 positive pDCs express significantly higher CD86 (Wilcoxon matched pairs test: p=0.0006, n=16) but not CD83. Functionally, Siglec-1 positive pDCs fail to express intracellular IFN-α via TLR-7/TLR-9. SLE patients reveal higher percentages of Siglec-1-positive pDCs (7.69±0.6 vs. 5.96±0.51; p=0.04), but lower Siglec-1 expression levels in Siglec-1-positive pDCs (7.83±0.61 vs. 11.7±0.8, p= 0.001) than healthy donors. Siglec-1 positive pDCs in SLE correlate significantly with disease activity (rS=0.55, p=0.008, n=22). Furthermore, Siglec-1 expression is not induced *in vitro* by IFN-α but by influenza virus in human pDCs.
Conclusions. Human blood pDCs can be subdivided into two distinct subsets according to their surface expression of Siglec-1. Siglec-1-positive cells might arise from differentiation of Siglec-1-negative pDCs. Semi-mature Siglec-1-positive pDCs might have an adaptive, potentially tolerogenic immunological function with impact on SLE pathogenesis.

Key words: plasmacytoid dendritic cell, Siglec-1, systemic lupus erythematosus.

P2:22

ANTIDFS70 POSITIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER RHEUMATIC DISEASES

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Objective. Antinuclear antibodies (ANA) are useful in the identification of rheumatic autoimmune diseases (RAD) such as systemic lupus erythematosus (SLE). While some have diagnostic significance, antibodies to the dense fine speckled 70kD antigen (antiDFS70) seem to be more common in healthy individuals and non-rheumatic diseases (such as prostate cancer and atopic dermatitis); when associated to RAD, other specific autoantibodies (AAb) are typically present.
This study's purpose was to evaluate the presence of RAD in patients with positivity to antiDFS70.
Design and Method. From 3636 ANA screens by indirect immunofluorescence (IIF) performed during one year at a public health institution, 101 suggested antiDFS70 presence (dense-fine-speckled/homogenous pattern). After confirmation with an immunoblot assay, 41 positive patients' records were analysed, considering diagnoses and positivity for other AAb.
Results. Forty-one individuals, 25 female, with a mean age of 37,29 years (± 23,07 years) were included. 12 were under 18 years old.
From a total of 9 patients with RAD, 3 presented more specific AAb for: SLE (N=1), rheumatoid arthritis (RA) (N=1) and mixed connective tissue disease (N=1). Other 3, although only antiDFS70 positive, presented entities not necessarily associated with AAb: reactive arthritis (N=1), juvenile idiopathic arthritis (N=1) and seronegative spondyloarthritis (N=1). Three cases without any other AAb were identified: systemic sclerosis (N=1), RA (N=1) and undifferentiated connective tissue disease (N=1).
Other diseases, with possible but unconfirmed correlation to antiDFS70, were found: asthma (N=4) and autoimmune thyroiditis (N=3). The most prevalent diagnosis with autoimmune/auto-inflammatory background was type 1 diabetes mellitus (N=5).
Conclusions. Three patients contradict the trend to interpret isolated antiDFS70 positivity as RAD exclusion criteria. However, one must consider the small sample size, the retrospective format of the study and the nonuniformity of available results between patients.
ANA are reliable biomarkers for RAD, included in the 2012 Systemic Lupus Collaborating Clinics classification criteria for SLE. In IIF, fine-dense-speckled pattern (typical of antiDFS70) can be interpreted as homogenous and erroneously associated with SLE. Considering this, IIF testing without antiDFS70 screening, outside proper clinical suspicion, detects individuals with no consistent evidence or RAD. This leads to anxiety in patients, familiars and physicians, who can adopt inadequate treatments.

Key words: antiDFS70, systemic lupus erythematosus, rheumatic autoimmune diseases

P2:23

MAPPING TRIM21ALPHA-AUTOANTIBODY INTERACTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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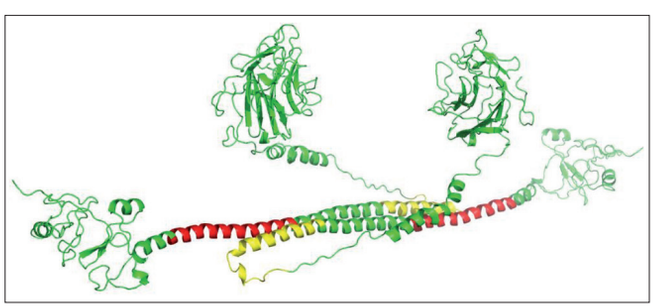
Objective. To analyze the molecular recognition of TRIM21 α and its autoantibodies in Systemic Lupus Erythematosus (SLE) patients.
Design and Method. Cross-sectional prospective study of 20 SLE patients diagnosed according to the SLICC-ACR2012 criteria, from the Rheumatology Department of La Fe Hospital. All patients showed high anti-Ro Ab (SSA) concentrations (>200,0 U/mL). We have also taken 8 healthy individuals as negative controls, who had anti-Ro Ab concentrations <15 U/mL. We studied the molecular recognition of TRIM21α by autoantibodies. To investigate the correlation of this antibody in respect to its epitopes, we mapped the dominant antigenic regions of TRIM21α, registering piezoelectric signal by a QCM-D sensor.
Results. Pre-steady-state analysis revealed an antibody bipolar bridging mechanism for SLE patients and healthy subjects. Identification of the main immunodominant human epitopes was finely mapped using series of overlapping synthetic polypeptides with a length of 21 aminoacids. The epitopes recognized by anti-TRIM21α spanned the linear sequence ELAEKLEVEIAIKRADWKKTVETQKSRIHAEFV (151-183 aa) for SLE patients and a novel conformational epitope for healthy volunteers. Sera of lupic patients was targeted by SLE epitope, allowing health subjects to be discriminated. MHC Class-II binding peptide prediction results corroborated the sequence as the immunodominant epitopes. The mostly coded allele was HLA DRB1*1304 and HLA DRB1*0806 for SLE patients and for controls, respectively. The subdominant epitope corresponded to the PRY-SPRY domain, which is a recently known mammalian Fc receptor. The TRIM21α three-dimensional structure was determined by homology modelling (Figure 1), confirming the proposed recognition mechanism: a dimeric structure of TRIM21α, with two antigenic hot spots.



Conclusions. In this work, we found that the host-guest chemistry of the TRIM21α protein is strongly dependent on the serum origin (patients and healthy subjects). Additionally, genetic and ethnic factors were associated to the allele DRB1*13:04. Furthermore, the proposed TRIM21α three-dimensional structure allowed to establish the TRIM21α functional mechanism, which is related to the NF-ϰB signalling activity. We show the key role of TRIM21α in regulating the immune response to infection, so that its malfunction may be significantly involved in the pathogenesis of SLE.

Acknowledgment
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Key words: TRIM21-alpha, molecular recognition, anti-Ro antibody

P2:24

ANTI-DSDNA ANTIBODIES ARE NOT CRITICAL TO DIFFERENTIATE CLINICAL PATTERNS IN SLE POPULATION: RESULTS OF TWO STEP CLUSTER ANALYSES OF A MONOCENTRIC SLE COHORT

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Objective. Systemic lupus erythematosus is a complex disease, characterized by multi-organ involvement and very different clinical pictures. In SLE, many targeting therapies are under consideration in phase II and phase III trials, and, recently, the first biologic treatment for SLE has been licensed (*i.e.*, anti-BAFF monoclonal antibody, namely belimumab). However, the best clinical target for these new therapies is far from clearly defined.
Design and Method. Consecutive patients were studied. Clinical and laboratory data were retrospectively analysed. Two step cluster analyses were performed.
Results. 366 patients were enrolled. They were 323/366 (88,3%) females, and 43/366 (11,7%) males. Mean age at study entry was 52,9±16,9 years. Follow-up was 5,3±3,9 years. The 1982 revised criteria for SLE (1) were fulfilled by 266/366 (72,7%) patients. Articular involvement was recorded in 282/366 (77%) patients, and a non-erosive/erosive arthritis was present in 137/366 (37,4%) patients; mucocutaneous involvement was documented in 268/366 (73,2%) patients, hematologic involvement in 216/366 (59%), renal involvement in 55/366 (15%), central nervous system involvement (including post-vascular lesions observed in cerebral MRI) in 88/366 (24%), serositis in 65/366 (17,8%), and finally, an antiphospholipid syndrome in 62/366 (16,9%). Anti-dsDNA antibodies were found in 112/366 (30,6%). More than two organ involvement was observed in 209/366 (57,1%) patients. Cluster analyses revealed three clinical different patterns: the first one characterized by the concomitant diagnosis of SLE and antiphospholipid syndrome, the articular and mucocutaneous as the prevalent involvements, and the positivity of antiphospholipid antibodies even without an antiphospholipid syndrome; the second one was the classical SLE picture with fulfilment of the 1982 revised SLE criteria, more than two organ involvement, and the articular, hematologic, and mucocutaneous as the prominent involvements, without antiphospholipid syndrome; the third one was the pauci-symptomatic SLE, characterized by the articular involvement and the absence of major organ involvement. Anti-dsDNA positivity did not distinguish one cluster from each other. Interestingly, different immunosuppressive treatments characterized the three clinical patterns: azathioprine or mycophenolate mofetil in the first one, cyclosporine-A of mycophenolate mofetil in the second one and methotrexate in the third one. The concomitant use of more than two immunosuppressors was observed in the second or in the third clinical pattern. The number of flare was higher in the second pattern and lower in the third pattern.
Conclusions. Three clear clinical patterns of SLE emerged from cluster analyses of our cohort of patients, and they were not influenced from anti-dsDNA positivity. Notably, this analyse could help to identify patients who represent the best target for new therapies.

Key words: systemic lupus erythematosus, cluster analyses, anti-DNA antibodies

P2:25

STUDYING THE POTENTIAL OF NEUTROPHILS FROM JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE) PATIENTS FOR PHAGOCYTOSIS

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Objective. Autoantibodies against nuclear antigens are present in Juvenile-onset Systemic Lupus Erythematosus (JSLE) patients and cause damages to several different organ systems, creating a variety of clinical symptoms.
Prolonged exposure to autoantigens is considered to be a consequence of impaired phagocytosis. A decrease in this function can lead to increased formation of neutrophil extracellular traps, also called NETosis and delayed clearance of apoptotic cells; both are thought to be the origins of autoantigens. It is therefore important to understand the potential of JSLE neutrophils to carry out phagocytosis. Nevertheless, the data published on this subject for neutrophils is only very limited, especially in juvenile-onset disease.
JSLE and paediatric control neutrophils showed differential expression of genes for phagocytosis in transcriptomic analysis performed by our group. Differential expression was observed for genes for receptors involved in recognition of pathogens (TLR-2), apoptotic material (AnxA3), microbial size (Dectin-1), opsonized material (CR3, FcγRIIIb), and adherence to and digesting of the target (CamK1D) as well as genes thought to promote phagocytosis (S100A9).
The aim of this study was to gain insight into the phagocytic potential of JSLE neutrophils by comparing the mRNA expression of relevant genes and phagocytic function in JSLE and paediatric healthy control patients.
Design and Method. Neutrophil RNA was extracted from children (diagnosed <17 years) with JSLE (n=9) and paediatric healthy controls (n=8). The mRNA expression of TLR-2, Dectin-1, AnxA3, CamK1D, FcγRIIIb, CR3 and S100A9 was measured using qPCR. The expression of β-actin and TBP was analysed as an internal standard.
For functional assays the neutrophils were incubated in 10% JSLE or control serum with E.coli, S.aureus and zymosan fluorescent particles and analysed using flow cytometry and confocal microscopy.
Results. Relative expression (normalised to housekeeping genes ± SEM) of TLR-2 (Control=0.21±0.03, JSLE=0.45±0.08, p=0.006) was significantly higher in JSLE patients compared to paediatric healthy controls. No difference was observed in CamK1D (p=0.54). Increased expression was observed in the JSLE group of CR3 (p=0.32), S100A9 (p=0.07), Dectin-1 (p=0.67), AnxA3 (p=0.19) and FcγRIIIb (p=0.14), although was not statistically significant.
Early preliminary data of confocal and flow cytometry analysis suggest an impairment in the neutrophil phagocytosis of S.aureus and E.coli in JSLE. This effect seems mainly due to factors in JSLE serum rather than an intrinsic effect of the cells, as incubation of JSLE neutrophils with JSLE serum shows less efficient uptake compared to control serum.
Conclusions. Expression of key genes involved in phagocytosis was shown to be increased in JSLE neutrophils compared to controls. The apoptotic burden which is observed in these patients might be causing this upregulation. Further experiments are being carried out to get a better understanding of weather this influences phagocytosis of pathogens in JSLE.

Key words: JSLE, neutrophil, phagocytosis

P2:26

IMMUNE RESPONSE (IMMUNOGENICITY AND SAFETY) IN PATIENTS WITH SYSTEMIC AUTOIMMUNE DISEASES AFTER PNEUMOCOCCAL CONJUGATE VACCINE

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Objective. Patients with autoimmune diseases are at increased risk against infections partly due to the underlying disease partly due to the treatment of it. The most effective way to prevent infection is the use of vaccination, supported by the guidelines of treatment of autoimmune diseases. In spite of the existing guidelines in practice has not always been prevailed the use of vaccines as a preventative approach in Hungary. There are few Hungarian data in the literature.

Further question could arise whether the vaccines (may) contribute to worsening or exacerbating the underlying disease. Another problem is that the response to the vaccine could be reduced and the success of vaccination can be dubious.
Design and Method. Our aim was to examine the immune response in patients with systemic autoimmune diseases (SLE, Sjögren sy) after pneumococcal conjugate vaccine in order to obtain information on vaccine immunogenicity and safety in this patient group.
This data may help strengthen the preventive approach and a safer patient care.
30 patients with systemic autoimmune diseases under immunosuppressant therapy (azathioprin, cyclophosphamide, methotrexate, methylprednisolon, and the combination of them) have been enrolled in our study. Before and 4 weeks after immunization blood samples were taken from the patients. Clinical state was evaluated by the clinical experts of the patients.
Pneumococcus specific IgG levels in the sera were measured by ELISA technic (The Binding Site), the test contains antigens of 23 serotypes. Levels of auto-antibodies relevant to the underlying disease (eg. ANA, ds-DNA, SS-A, SS-B) were measured from sera by ELSIA or indirect immunofluorescence technic.
Results. Prior to administration of vaccine the geometric mean of PCP IgG levels were 55.2 (40.7- 73.5) mg/l, while 4 weeks after vaccination it were significantly higher181 (36.1- 907) mg/l.
In case of 25 patients (82%) the immunogenicity of vaccine was appropriate, the PCP IgG level increased at least by two times, or exceeded 100 mg/l. In case of two patients (7%) the increase of PCP IgG level considered inadequate, in case of three patients (10%) it was considered uncertain. There was no sign which indicated the worsening or the flare of the disease. There was no deterioration in the levels of auto-antibodies after vaccination neither after 4 weeks nor subsequently. During the period of investigation (from two to eighteen months) invasive pneumococcal infection did not occur among vaccinated patients.
Conclusions. Our results are in accordance with literature data suggest that pneumococcal conjugate vaccine has good chance to induce appropriate immunogenicity and does not induce harm in patients with systemic autoimmune diseases under immunosuppressant therapy. Further studies and involvement of patients under biological therapy are required.

Key words: pneumococcal conjugate vaccine, immunogenicity, safety

P2:28

ACTIVATION OF THE STAT1 PATHWAY BY TYPE 1 AND 2 INTERFERONS AND SUBSEQUENT EFFECT ON NEUTROPHIL APOPTOSIS

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Objective. Juvenile-onset Systemic Lupus Erythematosus (JSLE) is a multisystem autoimmune disease characterised by the presence of autoantigens which result from increased numbers of apoptotic neutrophils. Serum from SLE patients contains high levels of type 1 (alpha and beta) and 2 (gamma) interferons (IFNs), which signal through the JAK/STAT pathway and thus activates STAT1. JSLE neutrophils have a more activated phenotype compared to healthy paediatric neutrophils and there are high levels of IFNs in SLE sera compared to age-matched controls; however the interaction between IFNs and neutrophils in regard to JSLE is yet to be elucidated.
Objective. To investigate the activation of STAT1 by type 1 and 2 IFNs and the subsequent effect on apoptosis of naïve and primed neutrophils.
Design and Method. Neutrophils isolated from healthy adult donors were either unstimulated or primed with TNF alpha (1ng/ml) for 30 mins. The neutrophils were incubated with IFN alpha (10ng/ml), IFN gamma (10ng/ml) or IFN beta (10ng/ml) for 15 mins or 6hrs. The activation of neutrophils was assessed by measuring expression of CD62L and CD11b and the percentage of apoptotic neutrophils was estimated using flow cytometry following Annexin V staining. Proteins were extracted, and pSTAT1 was analysed using Western blot. Wilcoxin test was used to analyse the differences in pSTAT1 expression.
Results. In neutrophils pre-treated with TNF alpha for 30 mins compared to unstimulated neutrophils CD62L expression was decreased (average geometric mean ± SEM; 5.52±0.03 vs 14.85±4.05, n=2) and CD11b expression was increased (217.5±41.5 vs 161±22, n=2) confirming that priming was taking place. All IFNs phosphorylated STAT1. However, the phosphorylation of STAT1 by IFN gamma was significantly increased in neutrophils pre-treated with TNF alpha compared to IFN gamma incubation alone (average ratio normalised to beta actin ± SEM; 4.4±2.5 vs 1.3±0.5, n=5, p=0.043). The level of neutrophil apoptosis was reduced in those incubated with IFN gamma for 6hrs compared to unstimulated (average % apoptosis ± SEM; 6.7±0.6% vs 16.7±1.7%, n=3). However, preliminary results suggests when the neutrophils were pre-treated with TNF alpha, this effect with IFN gamma may be abrogated (24.8%, n=1).
Conclusions. Here we show a differential effect between IFNs on neutrophil STAT1 phosphorylation in a naïve and activated phenotype, and a potential downstream pro-apoptotic effect of IFN gamma on neutrophils in a JSLE environment through the pre-incubation with TNF alpha. IFNs may contribute to the increase in neutrophil apoptosis, possibly via the increased phosphorylation of STAT1 in JSLE and which may contribute to the autoantigen increase that is fundamental to JSLE development.

Key words: neutrophil, apoptosis, STAT1

P2:30

SERUM 25-OH VITAMIN D IN TREATMENT-NAÏVE SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: RELATION TO DISEASE ACTIVITY, IL-17, AND IL-23

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Objective. Vitamin D (25(OH) D) has shown to modulate the innate and adaptive immune system. Autoimmune diseases have been linked to hypovitaminosis D. In SLE, the use of sunscreens, and corticosteroids therapy were mainly impeached. The current study aimed to evaluate the vitamin D status in treatment naïve SLE patients and its association with clinical and laboratory markers of disease activity including serum levels of IL-17 and IL -23.
Design and Method. A case-control study was conducted. Fifty-seven treatment naïve SLE patients along with 42 matched controls were included. SLEDAI score was used to assess disease activity. Serum levels of 25(OH) D, IL-17 and IL-23 were measured.
Results. Median level of 25(OH) D in SLE patients (40.8; 4-70 ng/ml) was significantly lower than controls (47; 25- 93 ng/ml) (p=0.001). 38.6% of SLE cases had 25 (OH) D levels <30 ng/ml (Hypovitaminosis D) versus 4.8% of controls (p<0.0001). The 25 (OH) D concentrations were significantly lower in patients with history of previous hospitalization than other patients (p<0.0001). There were negative correlations between serum 25(OH) D and serum levels of IL-17, IL-23 and ANA (rho= -0.5, -0.8, -0.5 and p<0.05) in SLE patients.
Conclusions. Hypovitaminosis D predicted autoimmunity in SLE patients. It seems to be a causal association rather than life style consequences.

Key words: systemic lupus erythematosus, 25 OH vitamin D, IL-17, IL-23

P2:31

VITAMIN D DEFICIENCY AND ANTI-C1Q ANTIBODIES AS MARKERS FOR DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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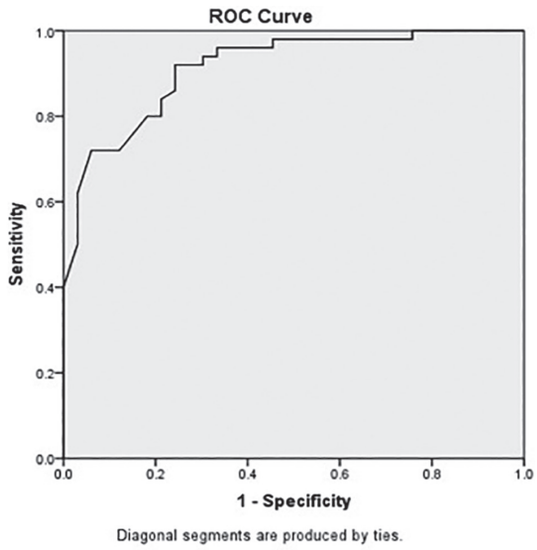
Objective. To measure the level of serum 25-hydroxyvitamin D3 [25 (OH) vit D] and anti-C1q in systemic lupus erythematosus (SLE) patients, and to evaluate the correlation between 25 (OH) vit D, anti-C1q and SLE disease activity especially renal activity.
Design and Method. Fifty SLE patients, diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for the classification of SLE 2012, and thirty-three age and sex matched healthy volunteers. SLE activity was assessed by systemic lupus erythematosus disease activity index (SLEDAI) and renal activity by renal SLEDAI. 25 (OH) vit D and anti-C1q were estimated by using ELISA kit.
Results: In the 50 SLE studied patients 25 (OH) vit D level was significantly lower in SLE patients (3.38±2.55 ug/L) compared to healthy control (5.36±2.88 ug/L) (p<0.002) while serum anti-C1q was significantly higher in SLE patients

(64.86±27.88 U/ml) compared to healthy control (30.15±13.93 U/ml) (p<0.000). 25 (OH) vit D was significantly correlated inversely with SLEDAI (p=0.01, r = - 0.361) and renal SLEDAI (p=0.021, r = -0.325). There was significantly positive correlation between anti C1q and SLEDAI (p=0.035, r =0.299) and renal SLEDAI (p=0.025, r =0.316). To quantify the diagnostic utility of anti-C1q by ELISA in SLE patients, a ROC curve was constructed for anti-C1q and SLE disease activity, the area under the curve (AUC) was 0.914, at cutoff 58 the sensitivity and specificity were 62.0% and 97.0% respectively, with positive predictive value (PPV) of 62.7%, negative predictive value (NPV) of 37.5% and 96.9% accuracy. By using ROC curve of 25 (OH) vit D at cutoff 1.05 the sensitivity for SLE disease activity was 90% while the specificity was 3.0% with AUC of 0.256.



Conclusions. Anti-C1q is a sensitive and specific indicator of SLE disease activity and renal activity, while serum 25(OH) vit D is sensitive but not specific for SLE disease activity.

Key words: SLE, anti-C1q, 25 (OH) vitamin D

P2:32

ANTI-TOPOISOMERASE 1 ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSOUS: RARE AND FOUND ONLY IN ANTI-DS DNA POSITIVE PATIENTS

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Objective. Anti-Topoisomerase 1 antibody (ATA) targets a DNA-linked protein and is considered a specific marker for Systemic Sclerosis (SSc). Some case reports and study of cohort reported the occurrence of ATA in up to 25% of patients with Systemic Lupus Erythematosus (SLE) (1), with a great variability related to the different methods employed (2). The purpose of this work is to analyze the prevalence of ATA in SLE with a CLIA assay and to correlate positive sera with other autoantibodies.
Design and Method. we collected 170 sera: 130 SLE and 40 controls (20 Raynaud's without the criteria for SSc, 10 SSc; 10 healthy subjects). All sera were tested with counterimmunoelectrophoresis (CIE) and CLIA BioFlash (IL diagnostics, San Diego, CA) for anti-ENA, ATA, anti-dsDNA and anti-chromatine antibodies. Antibodies to dsDNA were also tested by a radioimmunoassay (RIA, Farr assay; Kodak).
Results. Using CLIA, ATA was detected in 10 out of 170 sera (5.9%); while using routinely CIE ATA was detected in 6 out of 170 sera (3.5%). In particular: 6 were CLIA ATA+/CIE ATA+, 4 were CLIA ATA+/CIE ATA-; Cohen K agreement between the two for the global cohort reported a good agreement (K=0.73). The 6 CLIA ATA+/CIE ATA+ were all SSc patients, therefore analyzing only SSc patients, the agreement was perfect (K=1) while no CLIA ATA+/CIE ATA+ was found in SLE (K=0, no agreement). The clinical and demographic features of the 4 discordant sera (3 SLE and 1 Rayaud's) are reported in Table I.

Patients CLIA ATA+/CIE ATA-	Pt 4 M.M	Pt 1 O.O.	Pt 2 G.F.	Pt 3 A.F.
Race	Caucasian	African	Caucasian	Asiatic
Diagnosis	Raynaud's	SLE	SLE	SLE
ENA with CIE	Negative	U1RNP+Sm	U1RNP	Ku
ENA with CLIA	ATA	ATA	ATA	ATA
ds-DNA RIA IU/mL (ut off <7)	3.7 IU/mL	39 UI/mL	>700	24.8
ds-DNA with CLIA (IU/ml cut off ≤34,9)	12.9 IU/mL	>666.9 IU/mL	>666.9 IU/mL	27.8 IU/mL
Anti-chromatin (Concentration (Units)	Not available	139,517 (high positive)	136,08 (high positive)	29,05 (medium positive)
SLEDAI	na	4	10	6
Raynaud's Phenomenon	yes	No	No	yes
Puffy finger/sclerodactyly/fingertips ulcers	Puffy finger	No	no	No
Alveolitis/ILD/pulmonary hypertension	No	No	no	No
oesophageal dysmotility	No	No	no	No
Calcinosis/pitting scar/teleangectasias	No	No	no	no
Nailfold capillaroscopy changes	Negative	No	no	Scleroderma pattern active
DLCO reduction	No	No	no	Yes

Conclusions. in SLE ATA are detected in 2.3% of sera by a very sensitive CLIA but none was positive by CIE. Nonetheless we found a perfect agreement between the 2 assays for SSc and a very good agreement when other controls were tested. The 3 ATA positive SLE sera were also anti-dsDNA and anti-chromatin positive thus confirming the relationship between anti-DNA/DNA binding protein such as Topo-1. Interestingly only 1 out of the 3 patients developed a clinical picture resembling SSc even though not classifiable as SSc. We therefore conclude that further studies are needed to evaluate their clinical significance and can predict overlap between SSc and SLE.

Key words: anti-topoisomerase I, overlap, systemic sclerosis

P2:33

SEROPOSITIVITY FOR PREVIOUS EPSTEIN BARR VIRUS INFECTION IN THE SWISS SYSTEMIC LUPUS ERYTHEMATOSUS COHORT STUDY (SSCS)

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Objective. Mechanisms leading to systemic lupus erythematosus (SLE) are not well understood. However, previous studies suggested Epstein-Barr virus (EBV) infection to be essential for the development of the systemic autoimmune syndrome. In part, this view is based on observations that SLE patients are more frequently seropositive for EBV than controls. Our study aimed to explore the seroprevalence of EBV in a large Swiss cohort of SLE patients.
Design and Method. One hundred eighty SLE patients, fulfilling at least four classification criteria of the American College of Rheumatology, having a median age of 43 years (range 16-84, 86% females), a mean disease duration of 10.5 years and a median SLEDAI score of 4 at blood sampling, were analysed. Sixty-three age-matched normal blood donors (median age 46 years (range 19-81), 59% females) were used as controls. Sera were tested for EBV positivity by detecting IgG antibodies against Virus Capsid Antigen (VCA) and Epstein-Barr Nuclear Antigen 1 (EBNA-1) using commercially available ELISA kits.
Results. Numerically, 98.9% (178/180) of the SLE patients were seropositive for either anti-VCA IgG or anti-EBNA-1 IgG, compared to 95.2% (60/63) of the controls (OR 4.5, 95% Confidence interval (CI) 0.73 to 27.28, p=0.11). However, SLE patients were more often positive for anti-VCA IgG than controls (98.3% versus 92.1%; OR 5.09, 95% CI 1.18 to 21.95, p=0.0295). Moreover, positive anti-VCA IgG titers were significantly higher in SLE patients when compared to controls (p=0.0127). In contrast, seropositivity for anti-EBNA-1 IgG and positive titers were similar between SLE patients and healthy controls (91.7% versus 90.5%; OR 1.16, 95% CI 0.43 to 3.13, not significant for both).
Conclusions. In conclusion, we can confirm a trend towards increased seropositivity for EBV in SLE patients versus controls. Differences were clearest when analyzing seropositivity for anti-VCA IgG, but limited most likely due to a relatively small control cohort. Our data support the hypothesis of an important role for the anti-EBV response in the pathogenesis of SLE.

Key words: Epstein-Barr virus, anti-VCA IGG, anti EBNA-1 IGG, Swiss SLE Cohort Study (SSCS)

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AUTOANTIBODY RESPONSE TO TROVE2 IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Objective. To study the TROVE2: hIgG antigenic recognition mechanism from SLE patients and healthy subjects using a TROVE2-based QCM-D biosensor.
Design and Method. Cross-sectional prospective study of 20 SLE patients diagnosed according to the SLICC-ACR2012 criteria, from the Rheumatology Department of La Fe Hospital. All patients showed high anti-Ro Ab (SSA) concentrations (>200,0 U/mL). We have also taken 8 healthy individuals as negative controls, who had anti-Ro Ab concentrations <15 U/mL. A sensitive TROVE2-based QCM-D biosensor was developed.
Results. Pre-steady-state analysis revealed an antibody bipolar bridging mechanism for SLE patients and healthy subjects. The major linear epitope recognized by anti-TROVE2 spanned GGMALALAVTKYKQRNGWSHKDLLRLSH-LKPSSEGLAIVTKYITKGWKEVH sequence (aa 160-210) for healthy subjects. However, the major epitope in SLE serum is undiscovered. The difference between both epitopes corresponds to a majority necrosis-induced specificity in SLE patients, and an apoptotic pathway in healthy subjects. On the other hand, TROVE2 can be also used as a "YES-logic gate" capable of binding to Fcs, depending on alkaline earth cations in solution. Results suggest that the TROVE2-TRIM21α binding is a calcium-dependent protein interaction linked through the MIDAS-like motif in the vWFA-like domain.
Conclusions. A TROVE2-based QCM-D biosensor allows quantifying anti-TROVE2 antibodies in sera of SLE patients and healthy subjects at 0.05 U/mL level. The analysis of raw samples can be easily done since 40-fold dilution guarantees removing endogenous interactions due to the matrix effect.
The mechanism of hIgGs-TROVE2 interactions was defined as an antibody-bipolar bridging mechanism for SLE and healthy subjects. TROVE2 was also defined as a calcium-binding protein with a YES-logic gate involved in cell degradation processes which might be a crucial factor for development of SLE. Knowledge about this synergy may contribute to design novel metallodrugs, controlling the interaction that causes potential cellular damage.

Acknowledgment
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Key words: Trove2, QMC-D biosensor, calcium-binding protein

P2:35

FIRST CASE OF DISSEMINATED MYCOBACTERIUM GORDONAE INFECTION MIMICKING SYSTEMIC LUPUS ERYTHEMATOSUS EXACERBATION

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Objective. To present the first documented case of disseminated M.gordonae infection in a patient with systemic lupus erythematosus (SLE), mimicking exacerbation of the disease and posing unique diagnostic and therapeutic challenges.
Design and Method. Case description.
A 39 year-old imprisoned female patient, with SLE on corticosteroids and hydroxychloroquine,presented with fever of unknown origin (FUO). Her medical history included: thrombophilia (antiphospholipid syndrome, homozygous factor V Leiden, homocysteine gene deficiency), myocardial infarction, multiple deep vein thromboses and two pulmonary embolisms with inferior vena cava filter insertion. The patient had two long-lasting admissions, during which she was fully investigated for FUO (transthoracic cardiac ultrasound, serology, virology, full-body computerized tomographies, cultures, gallium scintigraphy, bone marrow examination) without any result, except from diffuse lung nodules that were attributed to the lupus. She also had arthritis of the metaphalangeal joints, a malar rash and a mild light-sensitive rash on light-exposed areas, possible evidence of lupus exacerbation. A18F-FDGPET-CT scan revealed high tracer uptake in the bone marrow, spleen, paratracheal and subcarinal lymph nodes and in pulmonary nodules, common findings in SLE. The dose of corticosteroids was increased and methotrexate was added, but the patient deteriorated, with a rise in temperature and spleen and pulmonary nodule enlargement. Bronchoscopy was negative and bone marrow biopsy showed a non-caseating granuloma. M. gordonae was isolated from an epigastric skin nodule biopsy (acid-fast stain, tissue PCR and culture) and also from peripheral blood (PCR, culture). This was considered to be a disseminated M.gordonae infection (Griffith DE et al, Am J RespCrit Care Med 2007; 175:367-416).
Results. Antimycobacterial treatment with levofloxacin, ethambutol, clarithromycin and rifampicin was initiated. The patient responded with defervescence and amelioration of her symptoms. All symptoms and signs of SLE also subsided.
Conclusions. Although M.gordonae is almost always considered nonpathogenic, when strict diagnostic criteria are fulfilled, it should be recognized as a definite pathogen in patients with FUO and underlying autoimmune diseases, such as SLE.

Key words: systemic lupus erythematosus, fever of unknown origin, atypical mycobacteria

P2:39

THE IMPACT OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To investigate the impact of HIV infection on the course and outcome of SLE.
Design and Method. A retrospective nested case-control study of SLE patients with HIV infection (HIV group) compared to an SLE HIV negative group (Control group). Seen at Chris Hani Baragwanath Academic Hospital. All patients met the 2012 SLICC classification criteria for SLE. Patients were deemed to have HIV based on the presence of either two positive ELISA tests with or without a confirmatory test or two positive HIV one being an antigen test (either PCR or viral load) and the other an antibody based test (ELISA and Western Blots). The groups were matched for age, follow up duration and presence of lupus nephritis.
Results. 40 of 543 patients who were tested for HIV were found to be positive, a further 5 patients had a false positive HIV serology. All except one patient were female (97.5%). The mean (SD) age at SLE diagnosis in the HIV group was 32.6 (11.5) years and did not differ significantly from the control group. The mean (SD) follow up duration was 8.9 (6.3) years which was not significantly different from the control group 7.6(5.7) years. 15 patients in both groups had lupus nephritis. 9 (21.95%) patients had a concomitant diagnosis of HIV and SLE, 26 (65.85%) were diagnosed with HIV after SLE and 5 (12.20%) before.
The table below shows the overall rate and reasons for admissions.

Admission rate, mean (SD), per 100 patient years of follow.up

Reason	HIV group	Control group	*p* value
Overall	67.5 (138)	53 (164)	NS
Lupus Flare	5 (21)	40 (163)	0.003
Infection	34 (80)	10 (16)	0.03
Lupus Flare and Infection	10 (63)	1 (3)	NS
Lupus related	0 (0)	2 (12)	NS
Other	18 (60)	4 (13)	NS

Respiratory infections were the most common cause of infection in the HIV and the control groups. 4 Deaths were reported in the HIV group, with infection contributing to all of them and one death in the control group was as a result of an oesophageal cancer.
Conclusions. HIV infection in SLE patients is a challenge because in both instances it affects young women. Our results suggests that HIV infection impact on the rate of admission related to infection and conversely there is a reduced rate of admission for flares. Deaths in the HIV group were mainly infection related.

Key words: HIV, SLE, Africa

Poster session 3: Genetics and pathogenesis of SLE

P3:40

MOLECULAR CHARACTERIZATION OF SLE BY RNA-SEQ: IDENTIFICATION OF GENES AND EXPRESSION-QUANTITATIVE TRAIT LOCI CONTRIBUTING TO PATHOGENESIS, SEVERITY AND TISSUE SUSCEPTIBILITY

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Objective. SLE is characterized by extraordinary immunological and clinical heterogeneity. Understanding the molecular basis of this variability is essential for risk stratification and application of targeted therapies. We undertook a robust transcriptome analysis in a well-characterized cohort of SLE patients to identify distinct molecular sub-phenotypes and explore the genomic variance contributing to disease severity.
Design and Method. Whole blood mRNA and genomic DNA were extracted from 142 SLE patients with varying levels of disease activity/severity and 48 matched healthy volunteers. Paired-end RNA sequencing was performed using the Illumina HiSeq 2000 platform and genotyping with the Infinium CoreExome followed by imputation from the 1000 Genomes. To integrate blood transcriptome with genotype and tissue-specific expression data we used the enrichment analysis of expression-quantitative trail loci (eQTLs) from the Genotype-Tissue Expression (GTEx) consortium and SLE GWAS loci using the Regulatory Trait Concordance (RTC) method.
Results. We found 6772 (5% False Detection Rate/FDR) differentially expressed genes (DEGs) between SLE cases and controls, with 4079 and 2693 genes been up– and down–regulated, respectively. Weighed co-expressed gene networks and molecular pathways were found to be associated with predisposition to SLE and disease severity. In the comparison of active lupus nephritis (LN) versus inactive LN, we identified genes involved in interferon signaling, chemotaxis of monocytes, cell cycle regulation, oxidative phosphorylation and complement response, to be over-expressed in active LN. On the other hand, most down-regulated genes were those related to extracellular matrix (ECM), ECM-receptor interactions, circadian rhythm regulation, dendritic cell maturation, angiogenesis and MAPK pathway. By integration of genotyping data, we mapped 3178 (5% FDR) genetic variants within 1Mb of the transcription start site of the gene, which were associated with gene expression levels (eQTLs) in SLE. We further identified SLE-specific eQTLs providing novel insights into genes and genetic variants contributing to its pathogenesis. Enrichment analysis of eQTLs from the GTEx consortium and SLE GWASs revealed several loci where the eQTL and GWAS signal were tagging the same functional variant across different tissues, thus providing insights regarding the most relevant tissues implicated in the disease.
Conclusions. Specific gene networks confer susceptibility to severe as compared to milder forms of SLE. Integration of blood transcriptome with genotype and tissue-specific expression data disclosed novel genes implicated in disease pathogenesis. These results may facilitate the molecular taxonomy of SLE patients into pathophysiologically and prognostically distinct subsets.

Key words: sequencing, molecular taxonomy

P3:41

TRANSCRIPTOME PROFILING BY NEXT GENERATION SEQUENCING OF HEMATOPOIETIC PROGENITORS IN MURINE SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. All blood cell lineages that have been implicated to the pathogenesis of Systemic Lupus Erythematosus (SLE) originate from the Hematopoietic Stem Cells (HSCs). We reasoned that the fundamental immune aberrations in SLE – genetic or epigenetic – may be traced back to the HSC population.
Design and Method. HSCs were isolated from either healthy C57/BL6 or NZBxNZW/F1 lupus prone mice bone marrow (n=15±5). The selection markers used are Lin-Sca-1+c-Kit+ for LSK compartment, including both long and short term HSCs. Flow cytometry cell sorting of the aforementioned populations was utilized for enumeration, RNA extraction and cell cultures. Paired-end RNA-sequencing analysis was performed with HiSeq 2000 platform.
Results. We identified significantly increased frequencies (~3% pre-diseased vs ~5% diseased, $p<0.05$) as well as absolute numbers (80-100×103 pre-diseased vs 100-150 ×103 diseased, $p<0.05$) of HSCs in the BM of lupus NZBxNZW/F1 mice with established disease as compared to young pre-diseased NZBxNZW/F1 or control C57/BL6 mice. Bone marrow populations such as hematopoietic stem progenitors cells (HSPCs), lymphoid and myeloid lineages differed in homogeneity depending upon either age or disease, suggesting alterations in HSC potential under inflammatory conditions. Accordingly, serum from F1 young mice promoted healthy HSCs to proliferation and skewed their differentiation towards myeloid lineage. Transcriptome analysis by RNA-seq of HSCs from lupus mice revealed 294 differentially expressed genes (DEGs) (FC>1.5, q<0.05) in diseased lupus mice compared to pre-diseased. DEGs show enrichment in transcription factors involved in hematopoiesis, regulation of immune responses, inflammation, autoimmune diseases, HSC function and homeostasis. We picked out three molecules for further investigation. Fbxw7 (FC -1,0) and Prdm1 (FC -3,0) are implicated in hematopoiesis. Prdm1 (Blimp1) is a pleiotropic transcription factor that plays crucial role in the differentiation towards lymphoid lineage (B and T cells). Fbxw7 is pivotal as it works like a "dual safety" device, which ensures HSC integrity in bone marrow niche. The third one is Ctla4 (FC 2,0), which is a well-known T-cell negative co-stimulatory receptor, but there is no indication of a functional role in HSCs. The involvement of these molecules in SLE will be assessed by functional analysis *in vitro* and *in vivo* in healthy and lupus prone mice.
Conclusions. A complex transcriptional network likely representing both intrinsic and extrinsic influences from the inflammatory microenvironment in the disease, governs the differentiation potential of hematopoietic stem cells in lupus leading to skewing towards the myeloid linage. These data provide a proof of the granulopoietic signature of SLE detected in DNA microarrays of bone marrow in SLE.

Key words: hematopoietic stem cells, molecular networks, transcription factors.

P3:42

DECREASED LUPUS MANIFESTATIONS IN PRISTANE-INDUCED MICRORNA 155-DEFICIENT MICE

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Objective. Deregulation of endogenous miR155 was observed in many autoimmune conditions, including systemic lupus erythematosus (SLE). We herein examined the role of miR155 in the development of systemic manifestations in mice with pristane-induced lupus (PIL).
Design and Method. MiR155-deficient and C57/Bl6 mice were injected with pristane or PBS as control and analyzed after 8 months. Glomerulonephritis and pneumonitis were quantified by using the composite kidney biopsy score (KBS) and by analyzing the numbers of affected lung-vessels and the area of the inflammatory lung-infiltrate, respectively. Specimens were stained with B220 (B), CD3 (T), Neu7/4 (neutrophils) and F4/80 (macrophages) and analyzed by cell-identi-

fication algorithms for nuclear segmentation (HistoQuest). Serum levels of anti-dsDNA, anti-histone and anti-chromatin antibodies were measured by ELISA. Frequencies of B cells, activated and regulatory $CD4^+$ T cells as well as Th1, Th2, Th17 cells were measured by flow cytometry. Quantitative real-time polymerase chain reaction was used to measure expression levels of interferon-signature and T-cell subset related as well as miR155-associated genes.
Results. All pristane-injected mice showed signs of pneumonitis, while controls did not. Compared to wild types treated with pristane, similarly treated knockouts showed significantly decreased perivascular inflammatory area with B cells being the most prominent inflammatory cell. Wildtypes had a more severe renal involvement in the KBS than knockouts. Corresponding with reduced organ involvement, miR155 deficient mice had significantly lower serum levels of anti-dsDNA antibodies, anti-chromatin and anti-histone antibodies and decreased frequencies of activated $CD4^+CD25^+$(Foxp3-) cells. Interestingly, also frequencies of $CD4^+CD25^+Foxp3^+$ regulatory T cells were lower in these mice. Upon restimulation, $CD4^+$ cells showed a more pronounced Th2 response in wild types, but no significant differences in Th1 and Th17 phenotype. Regarding INF-signature and T-cell subset activation, pristane-treated wild types showed significantly upregulated gene-expression patterns whereas equivalently treated mutants showed the same levels as PBS-treated controls.
Conclusions. MiR155 deficiency in PIL mice did not prevent disease, but was associated with less severe organ involvement, lower serum auto-abs levels, lower frequencies of Th2 cells, whereas lower expressions of genes jointly responsible for disease development may be one key mechanism. Thus, antagonisation of miR155 might be a future approach in treating SLE.

Key words: pristane induced lupus, micro RNA 155, SLE

P3:43

ASSOCIATION OF IRF5 POLYMORPHISMS WITH INCREASED RISK FOR SYSTEMIC LUPUS ERYTHEMATOSUS IN THE POPULATION OF CRETE, A SOUTHERN-EASTERN EUROPEAN GREEK ISLAND

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Objective. IRF5 (interferon regulatory factor 5) regulates type I interferon (IFN)-responsive genes, and has been one of the most consistently associated genes with systemic lupus erythematosus (SLE) outside the major histocompatibility complex (MHC). IRF5 haplotypes are associated with specific serologies in SLE patients, and the strongest reported SLE-risk haplotype in IRF5 is of Neanderthal origin. In this study, we sought to investigate whether IRF5 haplotypes are associated with risk for SLE in the genetically homogeneous Greek population of the island of Crete, as well as whether these haplotypes are associated with increased type I IFN in this population.
Design and Method. 322 SLE patients and 247 healthy, age- and sex-matched controls from Crete were genotyped for rs2004640, rs3807306, rs10488631 and rs2280714 SNPs of IRF5 gene. Genotyping was performed with Taqman primer-probe sets by using a Real-Time PCR platform (Applied Biosystems, ViiA™ 7 Real-Time PCR System). Odds ratios (OR) and 95% confidence intervals (CI) were calculated and the statistical difference in allele distribution was assessed by means of x2 test or Fisher's exact test. Haploview 4.0 software was used for haplotype analysis and for calculation of D' and r2 values.Haplotypes were inferred using the solid spine of LD method. Type I IFN levels were measured using a functional reporter cell assay.
Results. All IRF5 SNPs examined were found to be associated with SLE in univariate case-control analysis. In particular, the T, A and C alleles of the rs2004640, rs3807306 and rs10488631 SNPs, respectively, were associated with an increased susceptibility for SLE in the population studied (p<0.002 for each). These 4 SNPs formed 5 major haplotypes as has previously been observed in European ancestry. The Neanderthal-derived TACA risk haplotype was present in Crete and enriched in the SLE cases (OR=2.01, p=0.0003), but was present at a lower frequency than would be expected in Northern European populations (12.4% frequency in CEU HapMap population, 8.4% frequency in controls from Crete). This lower frequency of the TACA haplotype has also been observed in the southern European TSI HapMap population (9.1%), suggesting a North-South European gradient to this risk allele. Serum IFN levels were measured in a subset of the SLE patients, and carriage of the TACA IRF5 risk haplotype was associated with higher circulating type I IFN levels (p=0.037).
Conclusions. This study demonstrates the association of the Neanderthal-derived IRF5 haplotype with SLE susceptibility in the island population of Crete. While this allele was found at lower frequency in Crete than in Northern European populations, there was a strong genetic association observed, and patients carrying this allele had greater type I IFN, supporting a functional consequence of this polymorphism.

Key words: systemic lupus erythematosus, interferon regulatory factor, gene polymorphisms

P3:44

PHENOTYPICAL CHARACTERISATION OF THE OUTCOME OF HVEM-MEDIATED CO-STIMULATION OF B CELLS. A POTENTIAL MECHANISM INVOLVED IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Objective. Costimulatory receptors mediate T-cell–B-cell interactions that are important for the activation and differentiation of the latter. BTLA (B and T Lymphocyte Attenuator) is a novel membrane receptor with high-level expression on B-cells, which interacts with HVEM (Herpes Entry Virus Mediator) expressed on T-cells. We examined the expression and function of HVEM/BTLA and their potential contribution to the activated B-cell phenotype in SLE.
Design and Method. Baseline and induced expression of HVEM and its ligands, BTLA and LIGHT, were assessed by flow cytometry in B-cell subsets from SLE patients and healthy volunteers. Plate-bound HVEM.Fc chimeric protein was used to evaluate effects on cell proliferation (CFSE dilution), apoptosis (7AAD/Annexin), cytokine production and differentiation (CD27, CD38, IgD expression). Gene expression analysis was performed by qRT-PCR.
Results. Compared to healthy controls, active SLE patients displayed significantly upregulated HVEM on CD4+CD25- (mfi: 2.97±0.15 vs 2.19±0.18, p<0.01), $CD4^+CD25^+$ (97.8±1.3% vs 85.5±5.8%, p<0.05), and $CD4^+CD40L^+$ (95.2±1.5% vs 89.7±2.0%, p<0.05) T-cells. Patients and controls demonstrated comparable membrane expression of BTLA on all subsets of peripheral blood B-cells, whereas LIGHT was induced only after B-cell receptor (BCR) activation. In both SLE and control B-cells, HVEM crosslinking led to significantly reduced proportion of dividing (35±16% vs 60±9%, p<0.05) and apoptotic (49±6% vs 66±4%, p<0.01) cells, accompanied by 35% increase in anti-apoptotic Bcl-2 mRNA levels (p<0.05). Notably, HVEM crosslinking induced the differentiation of naïve CD27- B-cells, as evidenced by increased expression of CD27/CD38 markers ($CD27^+$: 25.4±4.1% vs 19.6±4.0%, p<0.01; $CD27^+CD38^{++}$: 4.3±0.9% vs 3.4±0.7%, p<0.05) and upregulation of the Pax5 transcription factor (by 39% in mRNA levels, p=0.005). IL-6 secretion was also significantly induced upon HVEM co-stimulation. Further experiments are underway to elucidate the molecular mechanisms of HVEM-mediated effects on B-cells and the potential use of HVEM/BTLA targeting in controlling lupus B-cell hyperactivity.
Conclusions. HVEM exerts significant B-cell co-stimulatory effects through regulation of proliferation, apoptosis and differentiation. Increased HVEM expression on SLE CD4+ T-cells might contribute to generation of aberrant B-cell responses in the disease.

Key words: costimulatory receptors, immune regulation, T-cells

P3:45

MARGINAL-ZONE-LIKE B CELLS IN PERIPHERAL BLOOD AS POSSIBLE BIOMARKERS OF HYPOSPLENISM/ASPLENIA IN SLE

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Objective. SLE is a disease associated with a risk of serious infections, in case of hyposplenism/asplenia incl. fulminant sepsis by encapsulated bacteria. For opsonization and phagocytosis of these agents are essential IgM natural Abs, produced by B cells of the splenic marginal zone. Is supposed, that investigation the changes of memory/marginal-zone-like B cell subpopulations ($CD19^+$ IgD^+ $CD27^+$ and $CD19^+$ IgM^+ $CD27^+$) in peripheral blood (PB) should be used as a putative biomarkers for detection a potential hyposplenism/asplenia of SLE in a prospective, comparative, and cross-over study.
Design and Method. Sixty adult SLE (ACR/1982, update in 1997) pts and 10 age- and sex-matched healthy controls (HC) were enrolled: infection, monoclonal gammopathy and renal failure in SLE were excluded. The DuraClone IM panel (Beckman Coulter) was used to identify $CD19^+$ IgD^+ $CD27^+$ and $CD19^+$ IgM^+ $CD27^+$ B cell subpopulations in PB samples by flow cytometry Navios (Beckman Coulter) with software analysis using Kaluza version 1.2.; data obtained were expressed in relative % of PB lymphocytes and absolute values x10-6/L. Parallel analysis of serological SLE biomarkers included C3, C4, ANA/IF (maximal titre), ANA/ELISA, anti-dsDNA/IFCL (maximal titre), anti-dsDNA/ELISA, and antinucleosome Abs. Data obtained were statistically processed using Medcalc-Statistical Software programme. In addition, identical B cell subpopulations were repeatedly investigated in two SLE after splenectomy.
Results. Significant differences ($p<0.001$) were obtained between absolute values of $CD19^+$ IgD^+ $CD27^+$ B cells (median 5.02, 95%CI 3.24-8.15) in SLE and HC (median 19.24, 95%CI 14.22-30.22) and also between absolute values of $CD19^+$ IgD^+ $CD27^+$ B cells (median 10.67, 95%CI 6.01-15.20) in SLE and HC (median 31.36, 95%CI 21.49-63.35); not significant differences were found in analyses using relative % of PB lymphocytes ($p>0.05$). In SLE was found a slight significant correlation (r -0.28, $p=0.03$) between absolute values of $CD19^+$ IgD^+ $CD27^+$ B cells and anti dsDNA/ELISA test. In two SLE after splenectomy the profound defficiency of marginal-zone-like B cell subpopulations under study was found.
Conclusions. The data obtained are suggesting that investigation of marginal-zone-like B cell subpopulations in peripheral blood should be useful as biomarkers of hyposplenia/asplenia in SLE, but further studies are necessary.
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Key words: systemic lupus erythematosus, marginal-zone-like B cells, hyposplenism/asplenia

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MILK FAT GLOBULE EPIDERMAL GROWTH FACTOR 8 GEN-ETIC POLYMORPHISMS IN KOREAN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by impaired clearance of apoptotic cells. Milk fat globule epidermal growth factor 8 (MFG-E8) is a protein connects between phagocytic macrophage and phosphatidylserine (PS) of apoptotic cell surface. Previous studies have reported that MFG-E8 deficiency causes lupus-like disease in murine models. However, MFG-E8 serum level was reported to be elevated in SLE patients. In this study, we determine whether genetic variation of MFG-E8 gene associated with SLE.
Design and Method. We collected the blood samples from SLE patients (n=280) and normal controls (NC, n=260). SNPs were genotyped by two steps. At first, we used polymerase chain reaction (PCR) in 55 SLE patients and 30 normal controls (NC) for a whole sequencing of MFG-E8 gene in Korean population. Then we used Taq-man probe assay in 225 SLE patients and 230 NC for genotyping of targeted 5 SNPs. For the PCR arrays, we extracted genomic DNA from whole blood. Also, we collected the all SLE participant's clinical characteristics, laboratory and drug data. All of results analyzed using SPSS 22 statistical program.
Results. Total five SNPs were genotyped in whole blood using PCR and Taq-man probe array. All SLE patient's mean age was 35.7±7.8 years and 92% were women, which is not different form NC (28.1±7.4 years and 93%, respectively). The MFG-E8 gene rs2271715 and rs3743388 polymorphisms were significantly different in the genotype frequency between SLE and NC. Moreover the rs2271715's T allele and rs3743388's major allele (C and G respectively) were significantly more common in patients with renal disease and associated with higher cumulated dose of mycophenolate mofetil and methylprednisolone. Also, the rs1878326 and rs1878327 polymorphisms were associated with CRP, anti-dsDNA level, and SLEDAI score.
Conclusions. Our data suggest that MFG-E8 rs2271715 and rs3743388 polymorphisms are associated with disease susceptibility and phenotype of SLE in Koreans. Also, rs1878326 and rs1878327 polymorphisms may be a marker of disease activity.

Key words: MFG E8, genetic polymorphism, lupus

P3:48

LONG TERM IMMUNOMODULATORY EFFECT IN CIRCULATING B CELL COMPARTMENT OF BELIMUMAB TREATED SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Objective. B lymphocytes plays a relevant role in the pathogenesis of Systemic Lupus Erythematosus (SLE). B cells are a target for new therapeutic strategies in the disease. Belimumab is a humanized monoclonal antibody targeted against B lymphocyte stimulator (BLys). In this work we evaluated the long term effects of belimumab treatment in SLE patients. Distribution of circulating naïve, effector without or with isotype switching, plasmablasts and memory $CD19^+$ B lymphocyte cells were analyzed in belimumab treated and untreated SLE patients before and along 6 and 18 months of follow up.
Design and Method. Fourteen SLE active patients, seven treated with belimumab, and age- and sex-matched healthy subjects were studied in parallel. Peripheral blood was obtained at basal conditions and 6 and 18 months of treatment. PBMC were obtained by Ficollhypaque density gradient centrifugation. Multiparametric flow cytometry analysis with the next labeled antibodies against the B cells surface antigens anti-CD19, CD27, IgD, CD38, CD40, CD23, HLA-DR were performed. We acquired in a FacsAria II flow cytometer and analyzed by Diva and Flow-Jo software.
Results. SLE belimumab treated patients showed a significant ($p<0.05$) decrease in circulating $CD19^+$ B cells with respect to non belimumab treated SLE patients and healthy controls at 6 and 18 months of follow up. This reduction is explained by a significative decrease in the $CD19^+CD27^-IgD^+$ (Naïve) B cell subset. In contrast, we found a belimumab associated expansion of $CD19^+CD27^+IgD^-$ (effector with class-switch recombination) and $CD19^+CD27Hi^+IgD^-$ (plasmablasts) B cells subsets. However, we did not observe significant modifications in the $CD19^+CD27^+IgD^-$ (effector without class-switch recombination) B lymphocytes. Nevertheless, CD19+CD27-IgD- (memory) B cells are significantly elevated at 6 and 18 months with respect to the start of the belimumab therapy.
Conclusions. Belimumab therapy has a long term immunomodulatory effect in circulating B cell compartment of SLE patients. This effect is characterized by a retraction and subset redistribution of B lymphocytes, with a decrease of naïve B lymphocytes and an increase of effector B cells.

Key words: belimumab, B lymphocytes, flow cytometry

P3:49

INHIBITION OF *IN VITRO* B CELL MATURATION BY NEW CHEMICAL PROBES IN ASSAYS USING BLOOD CELLS FROM PATIENTS WITH SLE AND IIM

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Objective. Systemic inflammatory diseases, such as systemic lupus erythematosus (SLE) and idiopathic inflammatory myositis (IIM), have largely unknown etiology and represent a disease area with major unmet medical needs. Treatment often give a clinical effect, but not in all patients; and symptoms often remain. In collaboration with the Structural Genomics Consortium (SGC), we investigate *in vitro* cellular effects of chemical probes, which are drug-like small molecules that can enter cells and which selectively inhibit potential new drug targets at therapeutically relevant doses. The effects we investigate are of two types, 1) either effects on expression of molecules which have been shown to be of pathological relevance in systemic inflammatory diseases, or 2) novel effects using unbiased analysis of the proteome. We have investigated *in vitro* B cell effects of about 50 different chemical probes which bind and inhibit epigenetic enzymes and regulators, such as bromodomains and histone methyltransferases, as well as kinases and other intracellular protein targets.

Design and Method. Peripheral blood mononuclear cells (PBMC) from patients with SLE or IIM were incubated in presence of about 50 different chemical probes at 1 or 0,1 uM, under B cell stimulating conditions for 6 days. The culture medium contained a B cell stimulating cocktail including IL4, IL10, IL21, sCD40L and CpG. Cell viability was determined by flow cytometry using the live/dead marker viability IR® and B cell maturation was investigated using markers for memory B cells (CD27), plasma cells (CD38) and surface IgG. Secretion of IgG was quantified by ELISA.
Results. The percentage of memory B cells, plasma cells and IgG expressing B cells, as well as IgG secretion, was induced by the B cell stimulating cocktail. These parameters were suppressed by a set of the epigenetic probes, as well as by some of the probes targeting other intracellular proteins. A few of the probes decreased cell viability. Both B cells from SLE and from IIM were affected.
Conclusions. We have found a set of chemical probes, with documented target selectivity and potent inhibitory effects of these targets, which affect patient *in vitro* B cell maturation and secretion of IgG. Further analysis is required to better understand the pathways that are affected.

Key words: drug development, B cell maturation, epigenetics

P3:51

PLASMA FICOLIN LEVELS AND RISK OF NEPHRITIS IN DANISH PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Given the scavenging properties of ficolins, we hypothesized that variation in the plasma concentrations of the three ficolins may be associated with development of lupus nephritis (LN), type of LN, end-stage renal disease (ESRD) and/or mortality among patients with systemic lupus erythematosus (SLE).
Design and Method. SLE patients attending a Danish tertiary rheumatology referral center were included. Plasma concentrations of ficolin-1, -2, and -3 were determined and dichotomized by the median into high and low. LN was defined by clinical criteria; type of LN by renal biopsy; ESRD follow-up time was defined as time from onset of LN to development of ESRD or censoring at end of follow-up
Results. The study included 112 SLE patients with median disease duration of 8 years of which 53 (47%) had LN at the time of inclusion. During a median follow-up of 10 years, five patients developed ESRD. Sixteen patients died. ORs of LN were 1.2 (95% CI: 0.6-2.7), 4.1 (95% CI: 1.7-9.7) and 0.9 (95% CI: 0.4-2.0) for patients with low ficolin-1,-2 and -3 plasma levels, respectively. The distribution of histological classes differed between patients with high and low plasma levels of ficolin-1 (p=0.009). Patients with high ficolin-1 plasma levels had increased risk of ESRD. There was no association between levels of the analyzed plasma ficolins and mortality.
Conclusions. Low plasma ficolin-2 levels were associated with increased risk of having LN. High plasma levels of ficolin-1 were associated with the histological subtype of LN and development of ESRD.

Key words: lupus nephritis, end-stage renal disease, inflammatory mediators

P3:52

SIX MONTH CHANGE IN REGULATORY T LYMPHOCYTES IS ASSOCIATED WITH DECLINE OF PROTEINURIA WITHIN 5 YEARS IN LUPUS NEPHRITIS PATIENTS

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Objective. Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). Clinical features of LN patients may vary from asymptomatic microhematuria to macroscopic hematuria, different range proteinuria or reduced renal function. Factors predicting the outcomes are sought, especially in a long-term. T lymphocytes with regulatory properties (Tregs) have been shown to play a role in preventing autoimmunity and to be involved in LN pathogenesis. Therefore, the aim of our study was to assess the relationship between repeated measurements of Tregs proportions and renal function after 5 years in LN patients with different disease activity.
Design and Method. Forty-eight LN patients (44 females, 4 males) were enrolled. Their mean age, disease duration and activity (SLEDAI) at baseline was 41.1 years, 9.8 years and 8.3 points, respectively. LN diagnosis was based on the presence of proteinuria, hematuria or cellular casts or biopsy evidence of lupus nephritis according to the ISN/RPS 2003 classification of LN. Their blood was collected twice: at baseline and after 6 months for biochemical tests and Tregs evaluation. Flow cytometry was used for analysis of T cells populations in peripheral blood mononuclear cells. Tregs were identified based on the unique pattern of expression of receptors CD4, CD25, CD127 and intracellular FOXP3. Patients were followed-up for 5 years.
Results. The 6 month changes in proportion of CD4CD25high cells and their intracellular FOXP3 concentrations were significantly lower in patients who had smaller decline in 24 hours proteinuria during 5 years follow-up.
Changes in glomerular filtration rate and SLEDAI within 5 years did not correlate with single or repeated Tregs measurements.
Significant associations between Tregs and other clinical features were observed at the time points of measurements only and are presented in the table below.

Table. Associations of Tregs with clinical characteristics.

Subgroup of LN patients	Trg cells		p
Single measurement (baseline)			
eGFR > median 94.2 ml/min	CD4CD25 low% in CD4	↑	0.03
ESR > median 32 mm/h	FOXP3% in CD4CD25 high	↑	0.003
C3 > median 97 mg/dl	FOXP3% in CD4CD25 high	↑	0.004
C3 > median 97 mg/dl	GITR% in FOXP3% in CD4CD25 high	↑	0.009
Two measurements (6 months interval)			
delta C3 > median 1 mg/dl	delta FOXP3 MFI in CD4CD25 high	↑	0.007
delta C4 > median 0.9 mg/dl	delta FOXP3 MFI in CD4CD25 low	↑	0.001
age > median 43.5 ys	delta FOXP3 MFI in CD4CD25 low	↑	0.001

C: complement; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FOXP3: forkheadboxP3; GITR: glucocorticoid-induced tumor necrosis factor receptor; MFI: mean fluorescence intensity.

Conclusions. Our results indicate that measurements of regulatory T lymphocytes repeated in a 6 months interval may predict 5 years change in proteinuria in lupus nephritis patients.

Key words: tregs, proteinuria, lupus nephritis

P3:53

ANTIOXIDANT RESPONSE IS ALTERED IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH A HIGHER ACCUMULATIVE DAMAGE SCORE AND LONGER EVOLUTION

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Objective. To evaluate the influence of antioxidant response in disease activity, specific autoimmune profile or by organ or systems affected in SLE patients.
Design and Method. Cross-sectional prospective study of SLE patients according to the SLICC-ACR2012 criteria, coming from the Rheumatology Department of La Fe Hospital and Arnau de Vilanova Hospital. In all patients we analyzed the serum concentration of GSH and GSSG by UPLC-MS/MS, and superoxide dismutase (SOD) and total antioxidant capacity (TAC) measuring Trolox concentration by colorimetric methods. In patients was also made a complete blood-test, and clinical, treatment and biometric data by personal interview were collected. We have also taken 34 healthy controls. Biostatistical analysis was performed by the R software version 3.2.3.
Results. A total of 142 patients were evaluated; (94% women) with a mean age of 47.40 (12.84) and 9.99 (10.57) year-evolution of SLE. The mean SELENA-SLEDAI score for disease activity is 5.92 (5.07) and the mean SLICC-ACR score for chronicity is 1.04 (1.42). A total of 34 healthy controls were recruited (80% women) with a mean age of 40.86 (11.65) years old. We have found higher values of SOD, and lower GSH and GSSG levels in SLE patients than in healthy controls (p=0.001, p=0.03 and p=0.003 respectively), and TAC showed no differences between both groups. We observed a statistically significant relationship among lower levels of GSH and GSSG with accumulated damage assessed by SLICC-ACR (Adj.p=0.02 and Adj.p=0.04 respectively), and lower SOD values with longer disease evolution (Adj.p=0.04).
Conclusions. We observed a misbalance of antioxidant enzyme levels in SLE patients compared to healthy controls, but total antioxidant capacity remains unaltered. Data suggest a rise of oxidative stress in patients with a poor antioxidant response, related to a greater accumulative damage and longer evolution of the disease, which is consistent with the presence of comorbidities in these patients.

Acknowledgment
Financial support by GVA (GV15/83 project) is acknowledged.

Key words: antioxidant response, SLICC-ACR, disease evolution

P3:54

POLYMORPHISMS IN GENES IN THE IL-17 PATHWAY AND B CELL MEDIATED IMMUNE RESPONSE MODULATE THE DEVELOPMENT OF SPECIFIC AUTOIMMUNE MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which a complex interaction between genetic, environmental and immunological factors determines the susceptibility and the phenotype. Dysregulations in IL-17 pathway as well as in B-cell mediated immune response have been observed in SLE. We have recently demonstrated that polymorphisms in TRAF3IP2 gene are associated with susceptibility for SLE and can predispose for the development of pericarditis (1). TRAF3IP2 encodes for Act1, a molecule that acts as a negative regulator of B cell by inhibiting CD40-mediated signaling and as a positive signaling adapter in IL-17-mediated cellular responses. TRAF6 is essential for the IL-17/Act1-mediated activation of NF-kB, while CD40 is the target for the Act1mediated inhibition of B cell response. The primary goal of our study was to evaluate the association of polymorphisms in CD40, TRAF6 and TNFSF4 (OX40) genes with susceptibility to SLE. Secondary objectives were to assess the possible association of these polymorphisms with the clinical and laboratory features.
Design and Method. We recruited 315 Italian SLE patients and 278 healthy controls. Genotyping of rs4810485 in CD40, rs4755453 and rs5030437 in TRAF6, and rs2205960 and rs10489265 in TNFSF4(OX40) SNPs was performed by allelic discrimination assay. A case/control association study and a genotype/phenotype correlation analysis were performed.
Results. Deviations from Hardy-Weinberg equilibrium for the three SNPs were not observed. None of the studies polymorphisms was associated with susceptibility for SLE. Only CD40 rs4810485 was associated at genotypic (p=0.034) but not at the allelic level. Nonetheless, these polymorphisms seem to contribute to define disease phenotype. TRAF6 was associated with the presence of anemia (p=0.019, OR=1.96), rs2205960 of TNFSF4 was associated with the pericarditis (p=0.013, OR=2.14), and rs4810485 of CD40 with the presence of anti-SSB/La (p=0.014, OR=2.26) and lupus nephritis (p=0.024, OR=1.8).
Conclusions. We were not able to confirm previous association of TRAF6 and CD40 polymorphisms with susceptibility for SLE. However, such SNPs seem to influence the disease phenotype. In particular, it is of interest the association of rs4810485 in CD40 with lupus nephritis and the presence of anti-SSB/La. Indeed, the modulation of CD40-mediated T cell-dependent antibody response has already been associated with the development of anti-SSB/La in association with SLE-like nephritis in a mouse model (2), probably due to an uncontrolled B cell activation signal.

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Key words: IL-17 pathway, CD40, lupus nephritis

P3:55

DNA HYDROXYMETHYLATION IS ASSOCIATED WITH DECREASED ANTIOXIDANT RESPONSE IN SLE PATIENTS

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Objective. To analyse the association between DNA hydroxymethylation and antioxidant response, and the putative association with other clinical and autoimmune parameters.
Design and Method. Cross-sectional prospective study of 142 SLE patients according to the SLICC-ACR2012 criteria, coming from the Rheumatology Department of La Fe Hospital and Arnau de Vilanova Hospital. In all patients we analyzed the serum concentration of GSH and GSSG by UPLC-MS/MS, and superoxide dismutase (SOD) and total antioxidant capacity (TAC) measuring Trolox equivalents level by colorimetric methods. The global methylation and hydroxymethylation percentage was measured by colorimetric methods. In patients was also made a complete blood-test, and clinical, treatment and biometric data by personal interview were collected. We have also taken 34 healthy controls. Biostatistical analysis was performed by the R software version 3.2.3.
Results. A total of 142 patients were evaluated; (94% women) with mean age of 47.40 (12.84) years and 9.99 (10.57) year-evolution of SLE. The mean SELENA-SLEDAI score for disease activity is 5.92 (5.07) and the mean SLICC-ACR score for chronicity is 1.04 (1.42). A total of 34 healthy controls were recruited (80% women) with mean 40.86 (11.65) year-old. Results of antioxidant response, methylation and hydroxymethylation rate in SLE patients and healthy controls are shown in Table I.

Variable	SLE Patients Mean (SD) Median (1st, 3rd Q.)	Healthy controls Mean (SD) Median (1st, 3rd Q.)
5-mC (% total DNA)	0.1 (0.06) 0.1 (0.05, 0.11)	0.12 (0.06) 0.12 (0.07, 0.15)
5-hmC (% total DNA)	0.03 (0.02) 0.03 (0.03, 0.04)	0.05 (0.01) 0.05 (0.04, 0.05)
GSH (µg/mL)	0.04 (0.02) 0.04 (0.03, 0.05)	0.05 (0.02) 0.04 (0.03, 0.06)
GSSG (µg/mL)	0.05 (0.03) 0.04 (0.03, 0.06)	0.06 (0.03) 0.06 (0.04, 0.07)
GSH/GSSG	1.03 (0.42) 0.97 (0.72, 1.23)	0.88 (0.36) 0.81 (0.53, 1.21)
SOD (U/mL)	3.65 (1.78) 3.36 (2.17, 4.96)	2.73 (1.73) 2.01 (1.52, 4.08)
TROLOX (mM)	1.02 (0.32) 0.99 (0.78, 1.21)	1.21 (0.67) 1.18 (0.59, 1.92)

We observed a correlation between the methylation and hydroxymethylation rate (r=0.68; $p<0.0001$), being these values lower in patients than in healthy controls ($p=0.024$ for 5-mC and $p<0.0001$ for 5-hmC). We found statistically significant relationship among 5-mC levels and the interaction 5mC/5hmC with TAC values (Adj.$p=0.019$ and Adj.$p=0.002$ respectively) in SLE patients. Moreover, decreased SOD values are associated with lower rates of 5-mC and 5-hmC in SLE patients (Adj.$p=0.002$ and Adj.$p=0.023$ respectively) in SLE patients. Examining the combined effect of 5mC-5hmC there is a statistically significant effect in SOD (Adj.$p=0.005$) and TAC values (Adj.$p=0.002$).
There were also statistical differences in 5-hmC and 5mC-5hmC interaction with positive lupus anticoagulant (Adj.$p=0.024$). No differences in the levels of both 5-hmC and 5-mC according to the disease activity by SELENA-SLEDAI score, chronicity by SLICC-ACR score, years of disease, organ or systems affected, and any kind of treatment were observed.
Conclusions. Our study reveals lower 5-hmC levels in SLE patients than in healthy controls, and different antioxidant response according to 5-mC and 5-hmC in patients than in healthy controls. So it suggests that there is a tendency to an increased antioxidant response related to DNA hydroxymethylation processes, may be due to an increment of oxidative stress, and the physiopathology of SLE disease may have an influence in this relationship. Moreover, the differences in the epigenetic level in SLE patients with positive lupus anticoagulant may lead to that different clinical phenotypes have some influence in epigenetic modifications in SLE.

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Key words: DNA hydroxymethylation, antioxidant response, superoxide dismutase

P3:57

ENHANCED IL-7 RECEPTOR SIGNALING IN SLE PROMOTES T-HELPER CELL PROLIFERATION THROUGH UPREGULATION OF MICRORNA-182 AND DOWNREGULATION OF FOXO1

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Objective. Recent reports have shown dysregulated microRNAs (miRNAs) in murine models of lupus, among them increased expression of microRNA-182 (miRNA-182), which has been demonstrated to target the transcription factor FOXO1 in activated murine $CD4^+$ T cells, leading to spontaneous T cell activation and clonal expansion. Here we aimed to investigate the expression of miR-182 and FOXO1 in T cells from human SLE patients.
Design and Method. Expression levels of miR-182 were analyzed with RT-PCR in purified peripheral blood $CD4^+$ T cells from 9 patients with SLE and age/sex-matched healthy controls (HC). Multicolor flow cytometry was performed to analyze $CD4^+$ T cell expression for FOXO1, Ki-67, Foxp3, the interleukin-7 receptor-α (CD127) and phosphorylated STAT-5a (pSTAT5). Analysis of serum IL-7 levels was performed with ELISA in 27 SLE patients and HC. Induction of miR-182 was assessed *in vitro* after polyclonal T cell stimulation in the presence of IL-7, and inhibition of T cell proliferation investigated using mir-182 antagomirs.α
Results. MiRNA-182 was significantly upregulated in $CD4^+$ T cells from SLE patients compared to HC, while the FOXO1 expression was decreased. The percentage of proliferating Ki-67+ conventional Foxp3- $CD4^+$ T cells (Tcons) was significantly higher in SLE compared to HC (3.85% vs. 1.58%, $p<0.001$) and their basal pSTAT5 levels significantly enhanced, suggesting a recent stimulation with common gamma chain-signaling cytokines. SLE Tcons displayed decreased expression levels for the FOXO1 target gene CD127 (MFI 2021 vs. 2553, $p=0.049$) and serum IL-7 levels were significantly higher in SLE compared to HC (17.0 pg/ml vs. 10.2 pg/ml, $p=0.001$). *In vitro*, miR-182 could be induced by IL-7, and specific inhibition of miR-182 inhibited T cell proliferation and survival. γ
Conclusions. Our data suggest that enhanced IL 7R/STAT5 signaling mediates the induction of miR 182 expression, which promotes the proliferation of conventional Foxp3- T cells SLE. Collectively, our data provide new insights in the pathophysiology of T cell hyperactivity in SLE and identifies miR-182 as a candidate target for future therapeutic approaches.

Key words: proliferation, lupus, T cells

P3:62

PERIPHERAL BLOOD MIR-146A EXPRESSION LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS PATIENTS

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Objective. Microribonucleic acids (microRNAs) are a new class of small non-coding RNA that negatively regulate gene expression on posttranscriptional level. Altered expression of miR-146a has been linked to the pathogenesis of both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). miR-146a was found to be overexpressed in RA synovial tissue as well as peripheral blood mononuclear cells (PBMCs). Underexpression of miR-146a was found to contribute to alterations in the type I interferon pathway in lupus patients by targeting the key signaling proteins. The aim of our study was to evaluate the diagnostic value of peripheral blood (PB) expression levels of miR-146a in both RA and SLE patients.
Design and Method. 63 RA patients according to the 1987 ACR criteria and 40 SLE patients according to the 1981 ACR criteria were included in the study. miR-146a expression levels in whole PB samples were determined by PCR (SYBR Green technology). 32 healthy donors were used as controls. SPSS 20.0 was used for ROC curve and Spearman correlation analysis.
Results. miR-146a was overexpressed in 29 (46.03%) of the RA patients but its expression levels couldn't differentiate patients from HCs (p=0.365). In comparison to RA, PB miR-146a expression in SLE showed diagnostic accuracy for discriminating patients from HCs with AUC=0.711 (p=0.002) with 82.5% sensitivity and 56.2% specificity. PB miR-146a showed statistically significant correlation with the diagnosis of SLE (correlation coefficiency = 0.363).
Conclusions. According to our data PB expression levels of miR-146a could be used as diagnostic biomarker for SLE patients but larger study is needed to confirm these results.

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Key words: microRNAs, systemic lupus erythematosus, rheumatoid arthritis

P3:63

FREQUENCY OF SLE-ASSOCIATED AUTOANTIGEN-SPECIFIC CD4+ T CELLS CORRELATES WITH SLE DISEASE ACTIVITY

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Objective. The development of autoantibodies directed to nuclear components such as SmD1, RNP70, Histone, Ro and La is characteristic of SLE pathogenesis mediated by pathogenic B and plasma cells. The question whether $CD4^+$ T cells specific to the aforementioned autoantigens are also implicated in SLE remains unclear. Here we report the frequency of autoantigen-specific $CD4^+$ T cells in health and disease determined by generating libraries of polyclonally expanded $CD4^+$ T cells from SLE patients and healthy individuals.
Design and Method. 200.000 $CD4^+$ T cells isolated from the blood of active SLE patients (n=6), inactive SLE patients (n=6) and healthy individuals (n=6) were seeded in multiple micro-cultures containing irradiated feeder cells, PHA and IL-2 for two weeks. Expanded $CD4^+$ T cells were tested for their capacity to proliferate in response to autoantigens measured by [3H]-Thymidine uptake.
Results. The frequency of $CD4^+$ T cells specific to RNP70, Ro and La is significantly higher in SLE patients with active disease when compared to inactive SLE patients and healthy individuals. $CD4^+$ T cells specific to SmD1 and Histone are slightly more observable in SLE patients than in healthy individuals, although their frequency is not significantly different in health and disease.
Conclusions. In conclusion, we can quantify the frequency of SLE-associated autoantigen-specific $CD4^+$ T cells, which also correlates with the disease activity of SLE.

Key words: Autoantigen, $CD4^+$ T cells, SLE disease activity

P3:64

TRPC6 AND NEUROPSYCHIATRIC SLE: FROM BEDSIDE TO BENCH

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Objective. Systemic lupus erythematosus (SLE) is an autoimmune disease with protean clinical features that not infrequently comprise neuropsychiatric manifestations (NPSLE). Recent evidence from basic science studies underlines the emerging role of salt-water balance and electrolyte exchanges control in the development and maintenance of autoimmunity, but the specific impact of these processes in SLE is poorly understood. Little is also known about the pathogenesis of NPSLE as well as about the possible genetic determinants of this particular part of the SLE clinical spectrum. Transient receptor potential cation channel, subfamily C, member 6 (TRPC6), a sodium/calcium-permeable cation channel, has been extensively studied in the setting of ischemia reperfusion-injury and brain excitotoxicity and represents an intriguing candidate for genetic and pathophysiological investigation in SLE.
Design and Method. More than a hundred patients with SLE were genotyped for the rs7925662 single nucleotide polymorphic variant (SNP) of TRPC6 gene. Clinical data (including historical and present SLE clinical features, autoantibody profile, blood cell count, renal and liver function tests) were collected at time of venepuncture. Patients with NPSLE were classified according to the 1999 ACR classification. Peripheral blood mononuclear cells (PBMC) from CC and TT homozygotes were challenged with ionomycin ± laryxil acetate (a specific TRPC6 inhibitor) before and after addition of calcium. Inward calcium fluxes were measured by flow cytometry after staining with Fluo3 and Fura-Red.
Results. SLE patients carrying the wild-type rs7925662 TT genotype had an increased risk of developing NPSLE during follow-up. PBMC from TT patients showed a substantially higher channel activity when compared to those from CC homozygotes, irrespectively of disease activity and treatment status.
Conclusions. TRPC6 could be involved in the pathogenesis of SLE and influence the risk of developing NPSLE either through a direct enhancement of leukocyte activity or through a differential behaviour in neurons and leukocytes.

Key words: TRPC6, calcium, neuropsychiatric lupus

P3:66

PHOTOSENSITIVITY TO INDOOR LIGHTING IN DARK SKINNED LUPUS PATIENTS

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Objective. Ultraviolet radiation (UVR), mainly UVB and shorter wave UVA, is known to affect systemic lupus erythematosus (SLE) in up to 80% of patients with exacerbation of skin disease and less commonly systemic flare with weakness, arthralgia, fatigue and fever. The aim of this study was to assess the effects of UVR in a cohort of dark skinned lupus patients from sun and indoor light sources.
Design and Method. A survey was conducted on non-caucasian patients with a known diagnosis of SLE by (SLICC 2012 criteria) who were under regular attendance at a tertiary lupus clinic at The Royal London Hospital. Over a 3 month period in 2016 attendees to the clinic who reported oversensitivity to light were asked to complete a photosensitivity questionnaire.

Survey

1. Patient demographics
   Name:
   Age:
   Sex:
   Ethnicity:

2. Lupus disease spectrum:
   Renal:
   Non-renal:
      Photosensitivity: duration in hrs:
      Other non renal:
   Antibody profile:

3. Do you wear sun block? Y/N

4. *If yes*
   A. how many times a day?
   B. SPF? (15, 30, 50, 80)
   C. Do you wear it during winter?
   D. Do you wear it indoors?

5. Do you find your skin sensitive to indoor lighting? Y/N

6. *If yes*, what type of indoor lighting are you exposed to? (ligh bulbs, TV screens, computer screens)

Results. 53 patients participated. The average age of participants was 38 years and only 3 were of male sex. There were 23 Asians (from the Indian subcontinent), 27 Afrocarribbeans and 3 Orientals. 48 reported skin rashes on exposure to UVR described as a photosensitive rash, some of these patients reported other symptoms like pruritus, worsening fatigue, arthralgia and flu like symptoms. 25% (n=13) patients with cutaneous manifestations were sensitive to indoor lighting (light bulbs, computer screens and occasionally TV screens). Of these 13 patients, 6 reported sensitivity to light bulbs only and 7 sensitivity to both light bulbs and computer screens. The reaction was most commonly a macular facial rash which lasted up to 2 weeks post exposure. 92.5% (n=49) were ANA positive. 47% (n=25) of them had positive anti ds DNA antibodies and 30 %(n=16) were positive for anti Ro. 88% (n=47) of patients were aware of the need to use a high factor sun cream and were applying Sun Protection Factor 50 (SPF50). 19% (n=10) of all these patients reported wearing sun protection creams indoors.
Conclusions. Clinicians and patients should be aware that a significant proportion of dark skinned lupus patients (almost a quarter in our cohort) may be affected by artificial indoor lighting and may need counselling on measures such as indoor sun cream application, computer screen filters and light bulb covers.

Key words: UVR, photosensitivity, indoor lighting

Poster session 4: Biomarkers and imaging

P4:67

AN ULTRASOUND ASSESSMENT OF THE HAND AND WRIST IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Body
Objective. To describe and determine possible correlations between US abnormalities of hand and wrist and clinical findings in SLE.
Design and Method. 34 randomly selected SLE patients were enrolled in the study. Clinical examination and US evaluation (Gray Scale and Power Doppler (PD)) of the tendons and joints of hands and wrists, were performed bilaterally on both dorsal and palmar sides. Joint assessment was performed on all MCP and PIP joints as well as the wrist and tendon assessment included finger flexors, wrist extensors and flexors. The scoring for synovitis was based on the EULAR/OMERACT scoring system.
Results. Within the cohort, 93% of the patients were female; mean age and median disease duration were 45.7±11.73 years and 11.00±6.94 years, respectively. 67% of patients scored D on MS-BILAG. Inflammatory arthralgia was reported by 21% of patients, however less than half of them (43%) had clinical detectable synovitis. US examination revealed abnormalities in 76% of cases. Synovitis was present in 74% of patients (22% wrist; 15% MCP/PIP, 63% both); with a grade 2 and 3 synovitis in 29% cases. The grade 2 or 3 synovitis was associated with a higher age ($p<0.05$) but not with inflammatory markers or disease activity. Furthermore, patients with US proven grade 2 or 3 synovitis received a higher mean dose of prednisone (12.2mg/day vs 5.6mg/day). Grade 1 synovitis did not correlate with tenderness or joint swelling, nor with the global disease activity. Synovitis with PD abnormalities were present in 24% patients, but only a third had concomitant clinical synovitis. Bone erosions (>1mm) were observed in 24%, half located at the second and fifth MC heads and half at the styloid process of the ulna. The presence of bone erosions was associated with the presence of grade 2 or 3 synovitis. US identified tenosynovitis in 40% of patients, involving the wrist extensors in the vast majority of cases (80%), especially of the 2nd extensor compartment.
Conclusions. US examination detects significant synovitis of the hand and wrist in the absence of clinical findings, and reveals structural damage in a large number of patients. The grade 2 or 3 synovitis was associated with a higher age, and higher corticosteroid dose. Tendon involvement is frequent and shows a specific pattern: the involvement of wrist extensors. Thus, US seems to be a valuable tool to identify subclinical joint manifestations, may help monitoring of joint disease activity and modulate treatment strategies in SLE patients.

Key words: ultrasound, lupus, joint

P4:68

SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR 2 (STNFR2) AS A BIOMARKER OF KIDNEY TISSUE DAMAGE AND LONG-TERM RENAL OUTCOME IN LUPUS NEPHRITIS

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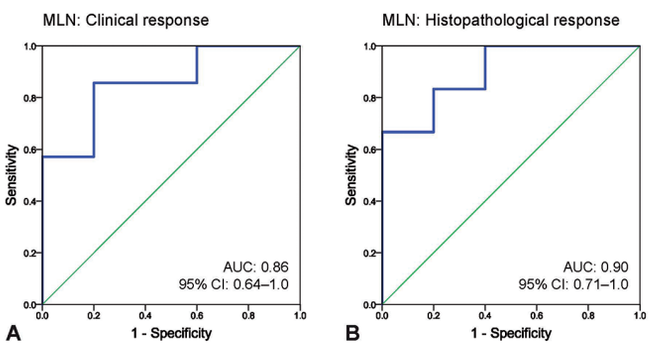
Objective. Accumulating evidence indicates the involvement of Tumor Necrosis Factor Receptors (TNFRs) in lupus nephritis (LN). We investigated the performance of soluble (s)TNFR2 as a biomarker of renal activity, damage, treatment response, and long-term outcome in LN.
Design and Method. Serum sTNFR2 levels were assessed in 64 patients with active LN (52 proliferative, 12 membranous), and post-treatment. Renal biopsies were performed on both occasions. Clinical responders (CR) were defined by at least 50% reduction in proteinuria, normal or improved eGFR, and inactive urinary sediment. Histopathological responders (HR) were defined by at least 50% improvement in renal Activity Index. Long-term renal outcome was determined by the Chronic Kidney Disease (CKD) stage after a median follow-up of 11.3 years (range: 3.3–18.8).
Results. Serum sTNFR2 levels decreased following treatment for LN (p<0.001). Baseline sTNFR2 levels correlated with Chronicity Index in both baseline (r=0.34, p=0.006) and post-treatment (r=0.43, p<0.001) biopsies. In membranous LN, baseline sTNFR2 levels were higher in CR (p=0.048) and HR (p=0.03) versus non-responders, and decreased only in CR (p=0.03). Consistently, high baseline serum sTNFR2 levels predicted both clinical (A) and histopathological (B) response to induction treatment in the membranous LN subgroup of patients (Figure). Long-term follow-up eGFR correlated inversely with both baseline (p=0.02, r=–0.29) and post-treatment (p=0.04, r=–0.26) sTNFR2. Both baseline (p=0.02) and post-treatment (p=0.03) sTNFR2 levels were associated with decreases in eGFR. Post-treatment sTNFR2 levels were higher in patients with a CKD stage of 3 or more than in patients with CKD stage 1 or 2 at last follow-up (p=0.008).



Conclusions. Our data suggest serum sTNFR2 as a non-invasive marker of kidney tissue damage and a predictor of long-term outcome in LN. Further evaluation of sTNFR2 as a predictor of clinical and histopathological outcome following treatment in membranous LN is merited.

Key words: lupus nephritis, biomarkers, TNFR2

P4:69

SERUM ANEXELEKTO (AXL) AS A NOVEL BIOMARKER OF RENAL ACTIVITY, TREATMENT RESPONSE AND LONG-TERM OUTCOME IN PATIENTS WITH LUPUS NEPHRITIS

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Objective. Anexelekto (Axl) is a receptor tyrosine kinase involved in the apoptotic cell clearance. We investigated serum Axl in lupus nephritis (LN) to clarify its role in renal disease activity, damage and treatment response.
Design and Method. Axl levels were assessed in 64 LN patients, before and after induction treatment. Renal biopsies were performed at baseline and post-treatment. Patients were classified as clinical responders (CR) or non-responders (CNR) based on the American College of Rheumatology response criteria, and histopathological responders (HR) or non-responders (HNR) based on changes in renal Activity Index. Long-term renal outcome was determined by the last Chronic Kidney Disease (CKD) stage, after a median follow-up of 11.3 years (range: 3.3–18.8).
Results. According to baseline biopsies, 52 cases were classified as proliferative and 12 as membranous LN. Baseline Axl levels decreased following treatment in CR (p<0.001) and HR (p<0.001), but not in non-responders, and were higher in HR versus HNR (p=0.003). High baseline serum Axl levels predicted histopathological response to induction treatment in (A) the entire cohort, (B) proliferative LN, and (C) membranous LN (Figure). Baseline Axl correlated with Chronicity Index in post-treatment biopsies (r=0.26, p=0.04), and inversely with baseline (r=–0.29, p=0.02), post-treatment (r=–0.31, p=0.01) and long-term (r=–0.29, p=0.02) eGFR. Baseline Axl levels were higher in patients with a CKD stage of 3 or more than in patients with a CKD stage 1 or 2 at last follow-up (p=0.03).
Conclusions. Our data suggest serum Axl as a candidate biomarker of renal activity, treatment response and damage accrual in LN. High baseline Axl levels were paradoxically associated with both histopathological improvement following treatment and an unfavourable long-term outcome. Our findings merit further investigation of the contribution of the Axl pathway to kidney tissue damage in LN.

Key words: lupus nephritis, biomarkers, Axl

P4:70

SERUM INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 2 (IGFBP2) AS A BIOMARKER OF CLINICAL AND HISTOPATHOLOGICAL TREATMENT RESPONSE IN LUPUS NEPHRITIS

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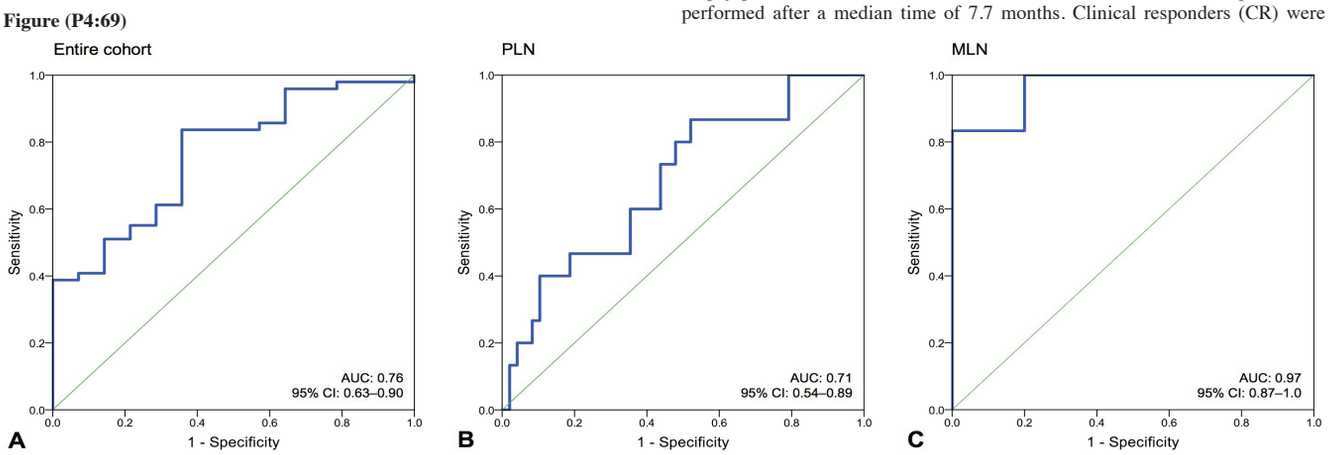
Objective. Insulin-like growth factor-binding protein 2 (IGFBP2) expression was found to be increased in anti-glomerular basement membrane glomerulonephritis and MRL/lpr lupus mice. We investigated the role of serum IGFBP2 in lupus nephritis (LN).
Design and Method. Serum IGFBP2 levels were assessed in 64 patients at a biopsy-proven LN and after induction treatment. Post-treatment biopsies were performed after a median time of 7.7 months. Clinical responders (CR) were

Figure (P4:69)



defined by at least 50% reduced proteinuria, normal or improved by at least 25% estimated glomerular filtration rate (eGFR), and inactive urinary sediment. Histopathological responders (HR) were defined by at least 50% improvement of Activity Index (AI).
Results. Serum IGFBP2 levels decreased following induction treatment in CR (p<0.001) and in HR (p<0.001), but not in clinical (p=0.44) or histopathological (p=0.16) non-responders. Post-treatment, but not baseline, IGFBP2 levels were higher in clinical non-responders versus CR (p=0.004), and correlated with AI (r=0.31, p=0.015) and Chronicity Index scores (r=0.35, p=0.006) in post-treatment renal biopsies, and with post-treatment SLE disease activity index 2000 (SLEDAI-2K) scores (r=0.32, p=0.009). Serum IGFBP2 levels correlated with proteinuria, both at baseline (r=0.34, p=0.006) and post-treatment (r=0.48, p<0.001). Despite an overall improvement in eGFR (p<0.001), baseline serum IGFBP2 levels were associated with decreases in eGFR following treatment (p=0.028).
Conclusions. Our data suggest serum IGFBP2 as a marker of renal activity and treatment response in LN. Post-treatment, but not baseline, levels mirrored both global SLE activity and histopathological findings, which together with the observed correlation with proteinuria levels suggests serum IGFBP2 as a marker of activity in patients with a history of LN and no or low-grade proteinuria following treatment.

Key words: lupus nephritis, biomarkers, IGFBP2

P4:71

THE EXPRESSION OF MICROPARTICLES IN THE BLOOD OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): PHENOTYPIC CHARACTERIZATION AND CLINICAL ASSOCIATIONS

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Objective. The goal of these studies is to elucidate the expression of microparticles (MPs) in the blood of patients with systemic lupus erythematosus (SLE). MPs, which are small membrane-bound vesicles released from activated and dying cells, contain a wide array of cellular macromolecules and have pro-inflammatory and pro-thrombotic properties which can impact on autoimmune and vascular diseases (VD). Previous studies exploring the expression of MPs in SLE have produced divergent results, thus affecting the interpretation of the potential role of MPs as disease mediators as well as biomarkers. To assess further the expression of MPs in SLE, we have therefore investigated the number, cellular origin and phenotypic properties of MPs in a large cohort of patients and controls.
Design and Method. 280 SLE patients and 280 individually matched population controls were characterized in terms of clinical manifestations, markers of systemic inflammation and autoantibody profile. Flow cytometry was used to detect MPs, evaluating size and binding of lactadherin as a measure of phosphatidylserine expression (PS+ vs. PS-). MPs were phenotyped according to cellular origin (platelet, endothelial or leukocyte) and expression of sCD40 ligand (CD40L), tissue factor (TF), vascular cell adhesion molecule-1 (VCAM-1), complement component 4 split product (C4d) and high mobility group box-1 (HMGB1).
Results. As shown by flow cytometry, levels of all MPs, regardless of origin and PS expression, were higher in SLE patients compared to controls (p<0.0001 for all). In the blood of SLE patients, PS- MPs were three times more common than PS+ MPs. The levels of PS- MPs were positively associated with female gender and smoking, and levels were decreased with impaired renal function. MPs expressing inflammation and/or activation markers (CD40L, TF, VCAM-1, HMGB1 or C4d) were increased in SLE patients (p<0.0001 for all). While levels of MPs were generally elevated in SLE, they were not correlated with SLAM index as a measure of disease activity.
Conclusions. The blood of patients with SLE has significantly higher levels of MPs of various cell origins compared to those of controls although these levels were not correlated with the SLAM index. These findings suggest dysregulation of hematopoietic and endothelial cells that may persist despite changes in disease activity. Since particle analysis can provide information on the state of diverse cell types, these studies suggest the utility of MPs as biomarkers to assess, on the basis of a single assay platform, diverse cell populations implicated in disease pathogenesis.

Key words: systemic lupus erythematosus, microparticles, microvesicles

P4:72

DE-CONVOLUTION OF WHOLE BLOOD TRANSCRIPTOMIC DATA FROM A PHASE IIB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ABATACEPT IN SYSTEMIC LUPUS ERYTHEMATOSUS

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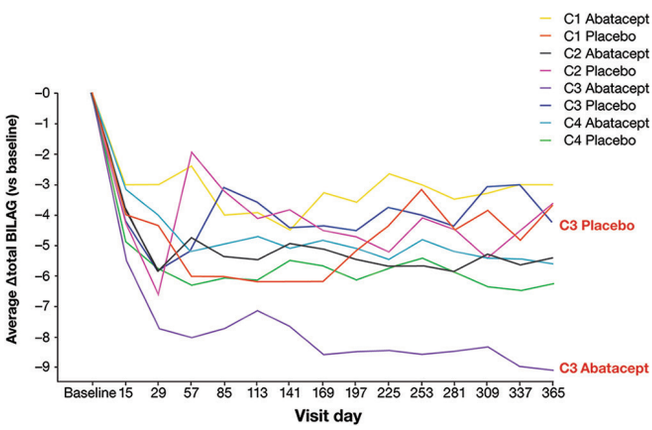
Objective. In this double-blind, Phase IIb trial, SLE patients with polyarthritis, discoid lesions or serositis were randomized 2:1 to receive abatacept (monthly ~10mg/kg; n=98) or placebo (n=46), following a month of high-dose corticosteroids and continuing background immunosuppression. To gain insights into responses to abatacept in pathologic subsets of SLE, a de-convolution algorithm was applied to patients' baseline transcriptomic data from whole blood mRNA.



Design and Method. Cell-specific marker genes, identified for key immune cell types (1) were used with a de-convolution algorithm (2) to identify cell proportions from baseline whole blood transcriptomic data, obtained by gene chip analysis of PAXgene mRNA from 144 patients and 10 healthy volunteers. De-convoluted patient-level data were used in an unsupervised analysis to generate consensus clustering for stratification. Patient clusters were used in a post hoc analysis of clinical study results.
Results. The primary study endpoints have been reported (3). Baseline levels of activated natural killer (NK) cells and neutrophils were higher in SLE patients versus healthy volunteers; NK and T helper (Th) cells were lower. At baseline, SLE patients were stratified into four major clusters, characterized by a dominance of: C1, Th cells; C2, plasma cells (PCs); C3, neutrophils, activated monocytes and activated dendritic cells; and C4, B or NK cells. Median and average total baseline BILAG scores were similar across all clusters and treatment arms. C2 (high PCs) contained most of the patients with high levels of anti-dsDNA. C1 was slowest to flare, regardless of treatment allocation (>170 days). In C3, abatacept-treated patients were slower to flare than placebo-treated patients (mean 194 vs 96 days) and had the largest decrease in total BILAG score and greatest treatment difference (Figure).
Conclusions. In a re-analysis of the Phase IIb SLE abatacept trial, baseline whole blood de-convolution identified four distinct immune cell phenotypic clusters, which demarcated clinical characteristics and response to therapy. Whole blood de-convolution might provide insights into specific immune cell-driven disease pathogenesis, thereby improving patient stratification and enriching trial data interpretation (4).

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4. Abstract reprinted from the ACR/ARHP Annual Meeting held November 6–11, 2015. The American College of Rheumatology does not guarantee, warrant, or endorse any commercial products or services. Reprinted by Bristol-Myers Squibb.

Key words: SLE, abatacept, biomarkers

P4:73

MIR-221-5P, MIR-380-3P, MIR-556-5P, MIR-758-3P AND MIR-3074-3P AS BIOMARKERS OF KIDNEY DAMAGE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To identify differentially expressed miRNAs circulating in plasma of patients with ldifferent stages of upus nephritis that potentially allow the diagnosis of renal damage in patients with systemic lupus erythematosus.
Design and Method. This is an observational studie (case-control and cross-sectional studies), in which we characterized the differential expression profiles of miRNAs in 14 samples from patients with lupus nephritis (LN), 8 samples from patients with lupus nephritis without (LSN) and 8 samples of healthy individuals (CTL) by Illumina. A group of miRNAs selected based on FC, p value, FDR and CPM were used to validate in 180 samples (100 patients with NL, 40 patients with LSN and 40 CTL) the results of renal biopsy.
Results. We found 16 miRNAs differentially expressed between patients with NL II vs CTL, 6 miRNAs differentially expressed between patients with NL III vs CTL, 67 miRNAs differentially expressed between patients with NL IV vs CTL, 10 miRNAs differentially expressed between patients with NL II vs LSN and 7 miRNAs differentially expressed between patients with NL II vs CTL. Then we increase the resolution to include as an additional criterion of discrimination on these 106 miRNAs differentially expressed, selecting those that present a Count Per Million (CPM) = 0, in CTL and LSN and CPM >0 in one or more groups of patients with lupus nephritis, the miRNAs that meet this criteria were: miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p. These five miRNAs thus experimentally validated by qPCR it presented a sensitivity averaged 97%, specificity 70.3%, positive predictive value 82.5%, negative predictive value 96% and 87.9% efficiency diagnosed. Whereupon we propose that these microRNAs are potential molecular biomarkers of kidney damage in patients with Systemic Lupus Erythematosus and request the patenting of the potential usefulness of these microRNAs diagnosed.
Conclusions. The miR-221-5p microRNAs, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p are potential diagnostic biomarkers of lupus nephritis in patients with systemic lupus erythematosus and the differential expression pattern of microRNAs have significant implications for the pathophysiology of renal damage in lupus nephritis patients.

Key words: biomarkers, miRNA, lupic nephritis

P4:74

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN AS A BIOMARKER FOR LUPUS NEPHRITIS

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Objective. Lupus nephritis (LN) has significant impact on the outcome of patients with systemic lupus erythematosus (SLE). One of the challenges of treating patients with LN is to accurately assess disease activity and predict its outcome. The aim of this study is to evaluate the role of urinary neutrophil gelatinase-associated lipocalin (uNGAL) in SLE patients as a biomarker of renal activity and flares.
Design and Method. Sixty eight patients were divided into three groups: the first group comprised 16 SLE patients with no renal disease, the second group 36 SLE patients with active renal disease, the third group 16 apparently normal volunteers. At the beginning of the study clinical and laboratory data including uNGAL were collected. All patients were followed up serially in visits. At each visit, urine samples were collected for measurement of uNGAL as well as for standard urinalysis and a urine albumine/creatinine ratio (uACR). Disease activity was assessed by the SLE disease activity indices. uNGAL levels were determined by ELISA, using spot urine.
Results. A highly significant difference was seen in uNGAL in all studied groups. Correlation was noticed between uNGAL and laboratory parameters of renal disease activity. There was a significant correlation between uNGAL levels and SLEDAI score (p<0,05) and uACR. Urinary NGAL showed a significant correlation with the activity (p<0,01) and chronicity indices (p<0,01) in LN patients.
Conclusions. Urinary NGAL can be a predictive biomarker that could be followed serially to forecast renal disease activity and lupus nephritis flare. Urinary NGAL may be a promising early marker for monitoring renal impairment in LN patients.

Key words: lupus nephritis, NGAL, disease activity

P4:75

URINARY NEUTROPHIL GELATINASE–ASSOCIATED LIPOCALIN (NGAL) AND MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1) AS BIOMARKERS FOR LUPUS NEPHRITIS IN COLOMBIAN SLE PATIENTS

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Objective. Our aim was to evaluate diagnostic value of urinary NGAL and MCP-1 as a potential markers for the diagnosis of LN in Colombian SLE patients
Design and Method. We examined levels of uNGAL and uMCP-1 in 93 consecutive SLE patients (ACR criteria 1982) from Hospital San Vicente Fundación, at Medellín, Colombia. uNGAL, uMCP-1 (R&D system, Minneapolis, USA) and serum anti-C1q antibodies (Inova, San Diego, USA) were measured by ELISA techniques. Several clinical and serological features were analyzed as well as disease activity (SLEDAI). Mann-Whitney tests were used to compare data and Spearman's rho for correlations. Additionally, ROC curves relating the specificity and sensitivity profiles of the 2 biomarkers were done.
Results. 93 SLE patients were recruited (88% female) with median age of 33.6±12.4 years and median disease duration of 11.5±14.8 years. Mestizo (75%) and Afro-latin American (22%) were majority. One quarter of patients had an early SLE (<2 years of duration) and 64 were admitted at the time of urine collection. Hematologic disease (89%), arthritis (83%), cutaneous involvement (82%), and renal disease (66%) were among most common manifestations. 63% of patients were positive for anti-C1q. We found significant positive correlation between uNGAL levels and SLEDAI (r=0.331, p=0.02) and between uMCP1 with SLEDAI (r=0.428, p<0.02) and with uNGAL (r=0.467, p<0.0001). uNGAL and uMCP-1 were significantly higher in patients with LN than in patients without LN (53.0±56.3 vs 16.0±16.6 pg/ml, p=0.001 and 2340.4±4521.4 vs 472.4±596.5, p=0.015, respectively). uNGAL levels were also significantly higher in patients with active LN (>500mg proteinuria/24 hrs) than in inactive LN (66.1±61.9 vs 9.0±8.6, p<0.001). A ROC curve constructed for uNGAL, uMCP-1, and anti-C1q for LN in all SLE patients showed a good level of sensitivity and specificity (Figure).

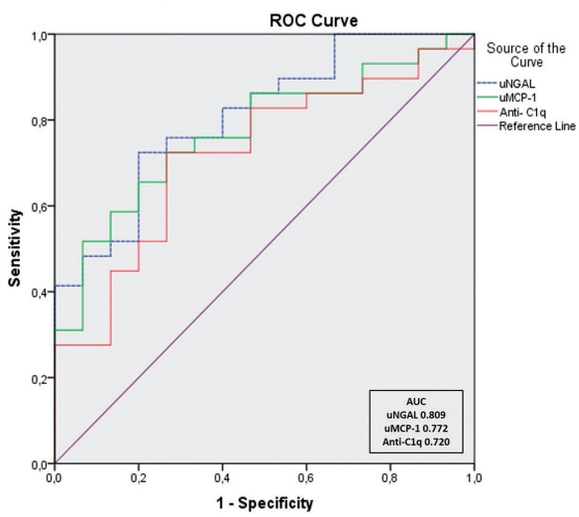

Figure. Receiver operating characteristic (ROC) curve of urinary NGAL, MCP-1 and anti C1q for the identification of LN (dotted line for uNGAL, solid green line for uMCP-1 and solid red line for anti C1q).

Conclusions. Colombian LN patients had 4 times and 5 times higher levels of uNGAL and uMCP-1, respectively, than patients without LN. Additionally, uNGAL was significantly higher in patients with active LN. Both markers were correlated with disease activity. uNGAL, uMCP-1 and anti C1q antibodies are good biomarkers for LN in Mestizo and Afro-Latin American SLE patients.

Key words: biomarkers, lupus nephritis, autoantibodies

P4:76

ANTI-C1Q LEVELS CORRELATE WITH DISEASE ACTIVITY IN A PROSPECTIVE FOLLOW-UP STUDY OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To estimate the overall association between antibodies against complement C1q (anti-C1q) and systemic lupus erythematosus (SLE) disease activity in a large prospective cohort of SLE patients in Switzerland.
Design and Method. In a cross-sectional study, clinical visits with accompanying serum sampling of 177 patients having been prospectively included to the multicentre Swiss SLE cohort study (SSCS) were analysed. Overall disease activity was determined using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Anti-C1q and antibodies against native DNA (anti-dsDNA) were measured using enzyme-linked immunosorbent assays.
Results. A significant correlation between anti-C1q levels and the SLEDAI (r=0.203, p=0.007) was found. In 155 of 177 patients anti-C1q levels could be directly compared with anti-dsDNA levels. In these patients, the correlation with the SLEDAI was stronger for anti-dsDNA levels than for anti-C1q (r=0.416 versus r=0.228 with p<0.0001 for both). In contrast, differences in autoantibody levels were more pronounced for anti-C1q than for anti-dsDNA when comparing patients with or without history of lupus nephritis, with or without hematuria (- or + versus ++ to ++++ hematuria) and with or without proteinuria (protein-creatinin-ratio > versus <0.2). In an explorative analysis, we also analysed a potential association of anti-C1q and anti-dsDNA levels with non-renal SLE manifestations. Significantly higher levels of both autoantibodies were found in patients with arthritis compared to patients without arthritis, but no associations were found with skin and central nervous system involvement, respectively.
Conclusions. In line with previous studies, our results suggest that anti-C1q could be used as a biomarker of disease activity in SLE, particularly in patients with lupus nephritis.

Key words: anti-C1q, SLEDAI, lupus nephritis

P4:78

ROLE OF THE PODOCYTES IN BIOMARKER PRODUCTION IN JUVENILE LUPUS NEPHRITIS

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Objective. Lupus nephritis (LN) is a severe manifestation of juvenile-onset systemic lupus erythematosus (JSLE); it occurs in up to 80% of patients and can lead to end-stage renal disease (ESRD) in 10-15% requiring dialysis or transplantation. LN is relapsing-remitting in character and each flare increases the risk of ESRD. LN is caused by the binding of autoantibodies present in the circulation to antigens expressed on native kidney cells leading to an inflammatory response. Previous data have identified urinary biomarkers (alpha 1-acid glycoprotein (AGP), caeruloplasmin (CP), transferrin (Tf), lipocalin-type prostaglandin D2 synthase (L-PGDS) and vascular cell adhesion molecule (VCAM)-1) in JSLE patients that indicate when a flare of LN is occurring. A deeper understanding of the pathways leading to biomarker release in the kidney and the effects these have on native kidney cells may identify new targets for therapy and thus potentially lead to a method of disease prevention in this organ.
Podocytes are specialised epithelial cells of the glomerulus that play important roles in selective filtration; they express toll-like receptors and the expression of receptors for TNF-alpha increase following inflammatory activation indicating they are potentially able to respond to cytokine stimulation.
This study aimed to determine the role of podocytes in the production of urinary biomarkers following exposure to pro-inflammatory cytokines.
Design and Method. Conditionally immortalised human podocytes (n=3/group) were cultured at 33°C until 70% confluent and then thermoswitched to 37°C for 10-14 days for differentiation to occur; these were then incubated with TNF-alpha, IL-1beta, IFN-alpha, IFN-gamma (10ng/mL) or LPS (1ug/mL) for 48 hours and RNA, proteins and culture medium were collected for analysis. Samples were analysed for biomarker production by qRT-PCR, western blot and ELISA analysis.
Results. Increased mRNA for CP was seen in response to IFN-alpha (0.593±0.227; p=0.05), a cytokine known to be increased in JSLE compared to healthy controls (0.019 ± 0.02); no changes in other biomarkers were present at the mRNA level. IFN-gamma (1688±133.2 pg/mL; p=0.02) and TNF-alpha (1643±250.9 pg/mL; p=0.04) treatment both led to an increase in the secretion of VCAM-1 into the culture medium compared to that seen in untreated podocytes (959.5±146.2 pg/mL); no other changes in protein were detected in the culture medium.
Conclusions. These data demonstrates that podocytes play a role in the production of CP and VCAM-1 during lupus nephritis and suggests these markers may be predictive of podocyte injury. However as not all the urinary biomarkers were expressed by podocytes. They are therefore not solely responsible for the production of urinary biomarkers in LN. Further work is required into the role that podocytes do play and into the roles played by other native kidney cells in urinary biomarker production in JSLE.

Key words: lupus nephritis, biomarker, podocyte

P4:79

DISCORDANCE OF AUTOANTIBODY RESULTS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: COMPARISON OF THREE METHODOLOGIES

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Objective. Production of autoantibodies is a hallmark of patients with Systemic Lupus Erythematosus (SLE). We compared Antinuclear Antibody (ANA) results by Immunofluorescence (IFA) with Enzyme Linked Immunoassay (EIA) results and with specific autoantibody results using a multiplex assay.
Design and Method. Samples (n=1000) were identified based on the ANA result obtained by EIA (BioRad). Samples were selected to be distributed across the range of the ANA (n=273 negative <1.0 U], 225 weak positive [1.1-2.9 U], 250 positive [3.0-5.9 U], and 252 strong positive [>6.0 U]. All samples were subsequently analyzed by IFA HEp-2 cells (Zeuss Scientific) and MIA on the BioPlex 2200 (BioRad). A sample was identified as positive for an ANA by the MIA if a positive result was obtained for at least 1 of the 11 included antigens.
Results. 67 patients with SLE were identified. Females made up 82% of patients and the mean age was 47 years (range 19-81 years).
On the IFA, 4/67 (6%) were ANA negative. On EIA, 2/67 (3%) were negative. These patients did not differ significantly from the entire group in terms of gender or age. Only one patient was negative on both the IFA and EIA. This patient had a positive SSA antibody on the multiplex assay. Comparison of IFA and EIA results are shown in the table below as the number of positive multiplex results/total.

		IFA¤			TOTAL¤
¤		≤1:40¤	1:80-1:160¤	≥1:320¤	
EIA¤	≤1¤	1/1·(100%)¤	0/1·(0%)¤	0/0·(0%)¤	1/2·(50%)¤
	1.1-5.9¤	1/2·(50%)¤	9/11·(82%)¤	7/10·(70%)¤	17/23·(74%)¤
	≥6¤	1/1·(100%)¤	5/5·(100%)¤	36/36·(100%)¤	42/42·(100%)¤
Total¤		3/4·(75%)¤	14/17·(82%)¤	43/46·(93%)¤	60/67·(90%)¤

A total of 60/67 (90%) were positive for one or more of the multiplex antibodies. DsDNA antibodies were borderline or positive in 36/67 (53%). Other positive antibodies found included antichromatin 35/67 (52%), SSA 33/67 (49%), sm-RNP 21/67 (31%), RNP 18/67 (27%), Smith 14/67 (21%), SSB 11/67 (16%), ribosomal p 9/67 (13%). and 1/67 (1%) SCl70.
Conclusions. There was some discordance between ANA testing by IFA and EIA in patients with SLE. However, all patients with SLE had at least one positive autoantibody if EIA, IFA and multiplex assay were done. We conclude that if a patient has clinical features of SLE, and is negative on one assay it is appropriate to perform the others. Conversely, if a patient is negative on all autoantibody tests then SLE is unlikely.

Key words: anitnuclear antibody, enzyme linked immunoassay, multiplex assay

P4:80

VITAMIN D, IL-10, IL-17, AND IL-23 AS BIOMARKER FOR DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Systemic Lupus Erythematosus (SLE) is a chronic, autoimmune, inflammatory disease and the prototype of multisystem autoimmune diseases. Several cytokines such as interleukin (IL)-10, IL-17, IL-23, and vitamin D have been suspected in the pathogenesis of SLE. However, the association between these cytokines, vitamin D and disease activity is unknown. We aimed to determine the association between IL-10, IL-17, IL-23, vitamin D and SLE disease activity index (SLEDAI) score.
Design and Method. We included 40 patients with SLE (mean age: 35.5±13.41 years, 95% female) and 20 healthy controls (mean age: 36.1±14.76 years, 70% female) in the study. Clinical and laboratory parameters and, SLEDAI score were evaluated. Serum IL-10, IL-17 and IL-23 were measured by nephelometry and vitamin D by HPLC (high-performance liquid chromatography). Mann-Whitney U and Kolmogorov-Smirnov test were used for statistical analysis. $p<0.05$ was accepted as statistically significant.
Results. The level of vitamin D was significantly lower (p=0,003), and IL-23 was significantly higher (p=0,001) in SLE patients compared to healthy controls. There was no significant difference for IL-10 and IL-17 between both group (p>0,05). However, a significant correlation between vitamin D and disease duration (p=0,02), and between IL-23 and vitamin D (p=0,019) were found among SLE patients. Vitamin D levels were correlated with SLEDAI score and IL-23 in patients group.
Conclusions. Although there are studies suppporting the role of IL-10 and IL-17 in the pathogenesis of SLE in the literature, there was no significant difference between patients and healthy controls in our study. IL-23 levels were significantly higher, whereas vitamin D levels were significantly lower in SLE patients than in the control group. Also vitamin D levels were negative correlated with duration of disease and IL-23. Levels of IL-23 may be used to evaluated the disease activity, or may be a promising therapeutic approach for SLE patients.

Key words: disease activity index, vitamin D, cytokines

P4:81

LOW PLASMA LEVELS OF FREE PROTEIN S ARE ASSOCIATED WITH CAROTID INTIMA-MEDIA THICKNESS, COMPLEMENT 3, AND LYMPHOCYTE COUNTS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Protein S has a role in the anticoagulation pathway and it mediates removal of apoptotic remnants. Atherosclerosis develops more frequently and earlier in individuals with SLE than it does in the healthy population, and it is a major cause of death in these patients.
Design and Method. We tried to assess the relationship between free protein S and subclinical atherosclerosis using Doppler ultrasound inspection of the carotid artery in SLE patients, combined with clinical features including disease activity markers.
Results. A total 111 female patients with SLE were recruited. The mean level of free protein S was 67.4±19.7%. After the patients were divided into three groups, according to their level of free protein S, the group with lowest level (<57%; low protein S) was compared to the other groups. In the low protein S group, haemoglobin and lymphocyte counts were significantly lower, erythrocyte sedimentation rates (ESR) were higher, and the patients were younger. The levels of complement protein 3 (C3) and 4 (C4) were also lower. Carotid intima-media thickness (cIMT) was lower in the low protein S group (3.78±0.8 vs. 4.2±0.84, p=0.012), while the proportion having carotid plaque was not different. Age, the levels of haemoglobin, C3 and C4, lymphocyte counts, and the ESRs, were found to be related to low free protein S status upon univariate logistic analysis. Following adjustments, lymphocyte counts, C3 levels and cIMT remained associated with low free protein S status.
Conclusions. When the group of SLE patients with a low level of protein S were compared to the other groups, their haemoglobin and complement protein levels, lymphocyte counts, ESRs and their cIMT differed. Moreover, the lymphocyte counts, levels of complement proteins 3, and the cIMT independently associated with low free protein S status.

Key words: protein S, disease activity, atherosclerosis

P4:82

PROTEOMIC ANALYSIS OF B6.NZMSLE1/SLE2/SLE3 FEMALE MICE KIDNEYS TOWARDS THE DISCOVERY OF LUPUS NEPHRITIS BIOMARKERS

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Objective. Systemic lupus erythematosus (SLE) is a complex autoimmune disorder affecting almost all organs and tissues. Renal involvement in SLE, known as lupus nephritis (LN), is one of the most serious and frequent manifestations, which is associated with a poor long-term prognosis. LN affects about two-thirds of patients during their life-time. At present, renal biopsy remains the standard method not only for establishing the diagnosis for LN, but also as a useful tool for assessing prognosis and monitoring therapy. However, it is an invasive procedure and has potential complications. Therefore, there is an urgent need for discovering reliable LN biomarkers with potential prognostic and diagnostic value. Using mass spectrometry (MS)-based proteomic approaches, we aimed to analyze alterations in the protein expression profiles of kidneys in a B6.NZMsle1/sle2/sle3 lupus mouse model, at different disease stages, in order to identify potential protein biomarkers that reflect *in vivo* immunological events of renal involvement in SLE.
Design and Method. Frozen kidneys of B6.NZMsle1/sle2/sle3 female triple congenic lupus-prone mice at different disease stages, 3 months (n=3), 5 months (n=3) and 9 months (n=3), and kidneys of C57BL/6 female control mice, 4 months (n=3), were used. Sections of 10 μm thickness were cut from frozen kidneys using a cryostat; these were used for subsequent protein extraction. Extracted proteins were purified, reduced, alkylated and digested with trypsin. Purified peptides were separated by liquid chromatography (LC) and analyzed by electrospray ionization quadrupole time-of-flight MS (ESI-QTOF-MS). Data were processed by Progenesis QI software.
Results. An average of 1600 proteins was identified. Several hundred proteins including immunoglobulins and complement component C1q were found to exhibit altered concentration levels in the lupus-prone mice compared to the control mice. Further pathway analysis, showed that some of these dysregulated proteins were implicated in important biological pathways including, apoptosis signaling pathway, JAK/STAT signaling pathway, and oxidative stress response, that are known to be associated with autoimmunity.
Conclusions. It is of interest that some of the detected pathways have been already implicated in SLE pathogenesis. Further work is underway in order to confirm these results in human clinical samples.

Key words: lupus nephritis, mouse model, proteomics

P4:83

ALTERATIONS IN THE ENDOCANNABINOID SYSTEM AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Endocannabinoid (eCB) system consists of a spectrum of endogenous lipid mediators (eCBs), like N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), along with their specific G protein-coupled type-1 (CB1) and type-2 (CB2) cannabinoid receptors, and the proteins responsible for eCB biosynthesis, inactivation, transport, and accumulation. Many recent studies have identified an important role of eCBs in immune system physiology and pathology. Particularly, AEA and the eCB-like molecule N-palmitoylethanolamine (PEA) seem to have anti-inflammatory properties, while 2-AG exhibits both pro-inflammatory and anti-inflammatory functions. CB2, more expressed in immune cells than CB1, seems to have a pivotal role in mediating the effects of eCBs on immune system. The objective of this study is to investigate the role of eCB system in patients with systemic lupus erythematosus (SLE) and matched healty subjects.
Design and Method. 13 patients with SLE and 14 healthy subjects were enrolled from outpatients clinic of Campus Bio-Medico University of Rome. Every SLE patient was positive for anti-dsDNA antibodies and/or exhibited hypocomplementemia with or without hypergammaglobulinemia, ENA or aPL positivity. None of them was treated with biological therapy at the time of enrolment nor with steroid bolus in the previous six months, while treatment with conventional immunosuppressants was allowed. SELENA-SLEDAI and BILAG were used to assess disease activity and SDI as damage index. AEA, 2-AG and PEA levels were quantified in plasma of SLE patients and healthy controls by using liquid chromatography-mass spectrometry (LC-MS). Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Paque (GE Healthcare). Gene transcription of CB1 and CB2 (Life Technologies) in PBMCs were quantified by real time PCR.
Results. No significant difference among ages was found in the two groups (SLE patients 37.2±7.8 years, healthy subjects 36.6±6.3, p=ns). In SLE patients, 73.3% of the subjects exhibited low C3, 40.0% low C4, 73.3% anti-dsDNA positivity; 26.7% of them were not taking glucocorticoids, 33.3% <5 mg of daily prednisone and 40.0% >5 mg of daily prednisone; 66.7% were taking conventional immunosuppressive treatment and 80.0% were taking hydroxychloroquine. SELENA-SLEDAI was 5.73±4.32; 6.66% of the patients exhibited at least 1 BILAG A and 60% at least 1 BILAG B; SDI was 0.73±1.16. eCB system was significantly altered in SLE patients. Plasma levels of 2-AG were significantly increased in SLE (5.12±2.60 pmol/ml) patients compared to healthy controls (2.8±1.088 pmol/ml, p=0.005), while no differences were found in AEA and PEA concentrations between the two groups. In SLE patients, we found a decrease of CB2 gene transcription in PBMCs compared to healthy controls (p<0.05), while no differences were found in CB1 gene transcription between the two groups.
Conclusions. Our results demonstrate, for the first time, an alteration of eCB system in SLE patients; these data may help to better understand the role of lipid mediators in SLE pathogenesis.

Key words: endocannabinoid system, lipid mediators, CB2 receptor

P4:84

NEXT GENERATION TESTING OF ANTINUCLEAR ANTIBODY (ANA) BY COMBINATION OF SCREENING AND CONFIRMATORY TESTING

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Objective. Purpose: According to international guidelines, the serological diagnosis of systemic autoimmune rheumatic diseases requires a two-tier approach starting with sensitive antinuclear antibody (ANA) detection by indirect immunofluorescence (IIF) on HEp-2 cells followed by characterization of positive findings with different immunoassays. A novel technique allowing the combination of screening and simultaneous confirmatory testing by a unique multiplex IIF reaction environment was developed to enable next-generation ANA testing for the first time.
Design and Method. Methods: ANA and autoantibodies (autoAb) to dsDNA, CENP-B, SS-A/Ro52, SS-A/Ro60, SS-B/La, RNP-Sm, Sm, and Scl-70 were determined by IIF and enzyme-linked immunosorbent assay (ELISA), respectively, and compared to simultaneous analysis thereof by second generation ANA analysis in patients with systemic lupus erythematosus (n=174), systemic sclerosis (n=103), Sjögren's syndrome (n=46), rheumatoid arthritis (n=36), mixed and undetermined connective tissue diseases (n=13), myositis (n=21), infectious disease (n=21), autoimmune liver disease (n=93), inflammatory bowel disease (n=78), paraproteinemia (n=11), and blood donors (n=101).
Results. There was very good agreement of next-generation ANA testing with classical one by IIF and ELISA regarding testing for ANA and autoAb to dsDNA, CENP-B, SS-B, RNP-Sm, Scl-70, SS-A/Ro52/TRIM21, and SS-A/Ro60 (Cohen's kappa >0.8, respectively). The agreement for anti-Sm autoAb was good (Cohen's kappa = 0.77). The differences of both approaches were not significant for autoAb to SS-B/La, RNP-Sm, Scl-70, SS-A/Ro60, and SS-A/Ro52/TRIM21 (McNemar's test, p>0.05, respectively).
Conclusions. Conclusions: Next-generation ANA testing can replace the two-tier analysis by combining IIF screening with multiplex confirmative testing. This addresses shortcomings of classical ANA analysis like false-negative ANA findings and lack of laboratory efficiency and standardization.

Key words: antinuclear antibody, digital fluorescence, next generation ANA testing

P4:85

ANTI-EPHRIN TYPE-B RECEPTOR 2 (EPHB2) AUTOANTIBODIES: A SPECIFIC AND SENSITIVE TOOL FOR SLE DIAGNOSIS IN LUPUS

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Objective. In a pilot ProtoArray analysis, 6 proteins out of 9483 were recognized by autoantibodies (AAb) from at least 10/20 patients with systemic sclerosis (SSc) compared to 0/18 healthy controls or patients with rheumatoid arthritis. Nevertheless, patients with Systemic Lupus Erythematosus (SLE) are known for high sera reactivity and overlapping AAb with SSc. We then propose to investigate whether the 6 candidates could be recognized by sera from SLE patients.
Design and Method. The 6 proteins Fibroblast Growth Factor 2 (FGF2), Allograft Inflammatory Factor 1 (AIF1), Ephrin Type-B receptor 2 (EphB2), Dual specificity protein kinase CLK1, Three prime Histone mRNA EXonuclease 1 (THEX1) and Ankyrin repeat and Sterile alpha motif domain containing 6 (ANKS6) were tested by ELISA on hundreds of controls and patients.
Epitope mapping was realized on proteins found as potential diagnostic markers.
Results. Among the 6 candidates, 2 proteins, EphB2 and THEX1, were significantly recognized by sera samples from SLE patients compared to all other controls including patients with SSc (respectively p=1.10-8 and p=1.7.10-8).
After epitope mapping for both proteins, we found, only for EphB2, a 15-mer peptide specifically recognized by 35% of sera samples from patients with SLE versus 5% of any other sera samples (N=157) (p<10-7). AAb titers were significantly higher in SLE sera (p<0.0001) and correlated with disease activity (p<0.02).
Conclusions. We have identified a peptide from EphB2 as a specific and sensitive tool for SLE diagnosis.
Interestingly, one of the major ligand of EphB2 (Ephrin-B2) has been involved in oncology as playing a crucial role in the formation of new vessels. As vascular inflammation and altered angiogenesis are observed in SLE, perspectives for this project are to test whether anti-EphB2 AAbs play a pathogenic role in the disease.

Key words: systemic, erythematosus, lupus

P4:86

SERUM FERRITIN AS A MARKER OF CLINICAL AND HISTOPATHOLOGICAL RESPONSE TO TREATMENT IN LUPUS NEPHRITIS

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Objective. Studies have reported elevated serum ferritin in active compared with inactive SLE, and associations with LN. We investigated the role of serum ferritin in LN.
Design and Method. Serum ferritin levels were measured in 64 patients with biopsy-proven LN (52 proliferative LN, PLN; 12 membranous LN, MLN), before and after treatment. Post-treatment renal biopsies were performed after a median time of 7.7 months. Clinical responders (CR) were defined by at least 50% reduced proteinuria, normal or improved by at least 25% estimated glomerular filtration rate (eGFR), and inactive urinary sediment. Histopathological responders (HR) were defined by at least 50% improvement of Activity Index in post-treatment biopsies.
Results. Serum ferritin decreased following treatment in the entire cohort (p<0.001) and in PLN (p<0.001), but not in MLN (p=0.35). In the entire cohort, ferritin levels decreased in CR (p<0.001), clinical non-responders (CNR; p=0.030) and HR (p<0.001), but not in histopathological non-responders (HNR; p=0.06). In PLN, ferritin decreased in CR (p<0.001) and CNR (p=0.003), as well as in HR (p<0.001) and HNR (p=0.011). In MLN, ferritin decreased in CR (p=0.03) and HR (p=0.046), but not in CNR (p=0.69) or HNR (p=0.89). In MLN, both baseline and post-treatment ferritin levels were higher in CNR than in CR (p=0.03 and p=0.005, respectively).
Conclusions. Our data suggest ferritin as a marker of histopathological treatment outcome in LN. In patients with MLN, high baseline ferritin predicted unfavourable clinical treatment responses, and, despite being initially lower, baseline ferritin decreased in CR, implying a role of ferritin in MLN and warranting further investigation.

Key words: lupus nephritis, biomarkers, ferritin

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DICKKOPF-RELATED PROTEIN 1 AND SCLEROSTIN LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of various autoantibodies and multiorgan involvements. The precise pathogenesis of SLE remains unclear. In recent years, the canonical Wnt/β-catenin pathway has been shown to play a role in inflammation. In patients with SLE, we aimed to determine serum and salivary levels of Dickkopf-related protein 1 (DKK1) and sclerostin those have important role in the regulation of Wnt signaling pathway.
Design and Method. 26 patients with SLE and 25 healthy controls were enrolled in the study. Fasting blood and saliva samples were obtained from the participants. Serum and salivary levels of DKK and sclerostin were measured by enzyme-linked immunosorbent assay. SLE Disease Activity Index (SLEDAI) and The Systemic Lupus Collaborating Clinics (SLICC) were recorded in patients.
Results. Serum DKK1 and sclerostin levels were lower in SLE patients compared to the controls (p<0.001 for both). However, their salivary levels were similar in SLE and control groups (Table). Serum DKK1 level was correlated with serum sclerostin level in the patient (r=0.783, p<0.001) and control (r=0.829, p<0.001) groups.
Conclusions. Serum DKK1 and sclerostin levels decrease in SLE. These results suggest that Wnt signaling pathway may be down-regulated in SLE.

Key words: Dickkopf-related protein 1, sclerostin, systemic lupus erythematosus.

Table. Serum and salivary DKK1 and sclerostin levels in the groups.

	HC (n=25)	SLE (n=26)	p-values
Mean age, years	32.1±8.1	37.0±9.9	0.57
Sex, % females	60	76.9	0.193
Hemoglobulin, g/dl	14.6±1.2	12.4±2.2	<0.001
WBC, 10^3/µl	7.4±1.9	6.2±2.5	0.59
Platelet, 10^3/µl	264.6±54.9	251.3±101.1	0.565
ESR, mm/hour	8.1±8.2	21.8±16.4	0.001
CRP, mg/dl	4.4±3.3	4.7±2.7	0.785
Serum DKK1, ng/ml	50.1±14.8	26.1±11.1	<0.001
Salivary DKK1, ng/ml	30.7±4.6	30.6±7.1	0.926
Serum Sclerostin, ng/ml	13.1±4.9	5.1±3.4	<0.001
Salivary Sclerostin, ng/ml	16.3±3.5	15.5±2.5	0.311

HC: healthy control; SLE: systemic lupus erythematosus; WBC: white blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DKK1: Dickkopf-related protein 1.

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THE IMMUNOLOGICAL PROFILE OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. A RETROSPECTIVE STUDY CONDUCTED DURING A THREE YEAR PERIOD

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Objective. The aim of this study was the correlation between immune markers in patients diagnosed with systemic lupus erythematosus or suspected to suffer from it.
Design and Method. 495 patients suspected to suffer were tested from 2013 to 2015.Antinuclear antibodies were determined by Indirect Immunofluorescence assay (IFA) and a substrate of Hep-2 cells. Anti-ds DNA antibodies were detected by IFA and a Crithidia luciliae substrate as well as by ELISA. Anticardiolipin antibodies (ACA), antibodies against beta2-glycoprotein and anti-ENA antibodies were detected by ELISA and the levels of C3 and C4 complement components were determined by Nephelometry.
Results. 265 (54%) out of 495 patients that were tested were ANA positive at a serum titer >=1/80 and mainly the fluorescent pattern detected was speckled (46%) as well as homogenous (29%) and nucleolar (11%). In 103 patients anti-ds DNA antibodies were detected by ELISA (39%) while anti- ds DNA antibodies were detected in 82 patients by IFA(31%). In 130 patients of the previous group (49%), IgG, IgM, IgA antibodies against beta2-glycoprotein (22%) were detected whereas in 42 patients (16%) ACA were detected. Anti-ENA were detected in 191 patients (72%) and mainly they were anti-SS-A (Ro), anti-RNP (38.7%), anti-SS-B (La) (32.1%) and anti-Sm (23.6%) positive.
In the group of 230 patients who were ANA negative (46%), there were patients positive to antibodies against beta2-glycoprotein (22%), presenting abnormal levels of C3 (76%) and C4 (22%) component complements, ACA positive (4%) and anti-ENA positive (14.3%).
Conclusions. The ANA positive patients presented mainly a speckled immunofluorescence pattern and only 30% of them were anti-ds DNA positive. There was a more frequent emergence of immunological markers such as anti-ENA antibodies, ACA, anti beta2-glycoprotein antibodies, abnormal C3 and C4 levels in patients who were ANA positive. There is a high proportion of patients (46%) who were ANA negative, yet positive to other immunological markers such as abnormal levels of C3 and C4 complement components (75%) or anti-beta2 glycoprotein antibodies (22%), a fact that could be attributed to the existence of a variety of clinical phenotypes of SEL as well as the possibility of a misguided primary diagnosis of the disease. It can be seen that these immunological markers can be helpful to the diagnosis or the detection of the activity of the disease, but none of them can be considered a specific marker without a correlation with the clinical manifestations of SLE.

Key words: ANA, anti-dsDNA, anti-ENA

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EVALUATION OF ACCUMULATIVE DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AS A NEW CARDIOVASCULAR RISK FACTOR

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Objective. To assess the cardiovascular disease (CVR) in SLE patients and the possibility of modifying it based on the accumulative damage and the disease activity.
Design and Method. Cross-sectional prospective study of SLE patients according to the SLICC-2012 criteria, from the Rheumatology department of La Fe Hospital and Arnau de Vilanova Hospital. All patients had a complete blood-test with autoimmunity markers, and clinical, biometrics and treatment data were also collected from the personal interview and the medical history. The biostatistical analysis was performed with the R software version 3.2.3.
Results. A total of 142 patients were evaluated; (94% women) with mean age of 47.40±12.84 and 9.99±10.57 year-evolution of SLE. The mean SELENA-SLEDAI index value for disease activity is 6±5.07 and the mean SLICC-ACR index value for chronicity is 1±1.42. 15% of patients had had some kind of CVD, with an increase of the classical cardiovascular risk factors comparing to the group who hadn't had any CVD manifestation.
We found a statistically significant association between high scores in the SLICC-ACR index (p<0.001), dyslipemia (p=0.04), diabetes (p=0.02) and the presence of CVD in our patients, and a tendency with the presence of hypertension, high levels of LDL-cholesterol and high scores in the SELENA-SLEDAI activity index. We also observed a marked tendency between levels of IgM anticardiolipin and IgM beta2-glicoprotein, finding higher levels in the group of patients that had suffered any manifestation of CVD.
Conclusions. The CVD rate among our group of patients is 15%, clearly higher than the general Spanish population (8.53%). We confirm the key role of classical cardiovascular risk factors as a trigger of CVD in SLE; however, the accumulative damage of the disease has a determinant paper in the cardiovascular risk of our patients. Therefore it could be proposed as an additional factor of cardiovascular risk in SLE patients.
The disease activity seems to have a tendency of correlation between higher SELENA-SLEDAI scores and the presence of CVD, though the years of disease evolution don't seem to influence in CVD.

Acknowledgment
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Key words: accumulative damage, cardiovascular risk factor

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ROUTINE URINE ANALYSIS FOR PROTEINURIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IS NECESSARY. A CASE PRESENTATION

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Objective. A routine urine analysis and the evaluation of proteinuria in patients with SLE is necessary since 50% of them will develop kidney disease.
To highlight the contribution of the laboratory department to the diagnosis and evaluation of kidney function in patients with SLE.
Design and Method. A 42-year-old patient showed up at the emergency department complaining for fatigue, debilitation and puffiness of the legs. The patient was diagnosed with SLE and renal disease 12 years ago. The renal biopsy which was conducted at that time revealed lesions of class IVb SEL diffuse proliferative glomerulonephritis with evidence of active nephritis and chronic disease (according to WHO). He was treated with a combination of drugs including cortisone and cyclophosphamide for a period of 3 years. During this period his renal function had been frequently evaluated and when it reverted to normal levels the treatment was ceased as well as the routine evaluation of the disease. The patient also mentioned that he had not been subjected to any clinical or laboratory evaluation during the last four years. The laboratory evaluation at the present time revealed normochromic normocytic anaemia and the hematocrit levels were 24.8%. The patient's laboratory testing also revealed: ESR: 139mm, low levels of complement, and renal impairment with high serum creatinine levels (3.2 mg/dl) and urea levels (234mg/dl) while the total protein levels of the serum were 4 g/dl, the albumin levels were 1.3 g/dl and there was also a high protein concentration in the urine. That is to say, nephritic range proteinuria was detected and 12.7 g of total protein was excreted in a 24h urine collection. The patient was positive to antinuclear antibodies up to a 1/320 dilution titer and the fluorescent pattern was homogenous .He was also positive to anti-ds DNA antibodies.
Results. The microscopic examination of the urine revealed a urinary sediment with nephritic and nephrotic elements: a lot of leukocytes, dysmorphic erythrocytes, many oval fat bodies some containing cholesterol crystals and many leukocyte, erythrocyte and fatty casts. The patient was retreated with cyclophosphamide and cortisone and he was subjected to clinical and laboratory follow-up of his kidney function.
Conclusions. Patients with SLE should be followed-up by the physicians and follow their instructions so as to avoid impairment of their kidney function. The main target of the treatment is the recession of the clinical manifestations of the disease and the improvement or at least the stabilization of the kidney function.

Key words: urine, proteinouria, kidney

Poster session 5: Old and new treatments for SLE

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A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, ASCENDING DOSE STUDY TO EVALUATE EFFICACY, SAFETY, AND TOLERABILITY OF CC 220 IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To evaluate the efficacy, safety and tolerability of CC-220 in subjects with systemic lupus erythematosus (SLE).
Design and Method. CC-220 binds cereblon and facilitates Ikaros and Aiolos degradation, thus reducing levels in B-cells, T-cells, and monocytes, and inhibiting plasmablast differentiation. Both Ikaros and Aiolos are required for B cell development, and have been associated with an increased risk of developing SLE. CC-220 was evaluated in subjects with active SLE in a Phase 2, double-blind, placebo-controlled, ascending dose study (NCT02185040).
42 adult SLE subjects with serological and clinical activity more than 6 months, and a baseline Hybrid SELENA SLEDAI (HSS) score at leat 4 were randomized 4:1 to one of four escalating doses of CC-220 or matching placebo. The four active treatments included CC-220 0.3mg QOD, 0.3mg QD, 0.3mg alternating with 0.6mg QD, and 0.6mg QD, for 12 weeks of treatment followed by 12 weeks of observation. Stable doses of corticosteroids (10mg prednisone or equivalent daily), non-steroidal anti-inflammatory drugs, and antimalarials were permitted. Efficacy assessments included HSS, Cutaneous Lupus Area and Severity Index (CLASI), and swollen (SJC) and tender joint counts (TJC).
Results. Baseline demographics included 39 females (92.9%), mean age 47.2 years, with 64.3% White, 31.0% Black, 2.4% Asian and 2.4% other races. Mean duration of SLE was 10.2 years, 31 (73.8%) had arthritis, 30 (71.4%) cutaneous disease, 21 (50.0%) alopecia, 4 (9.5%) mucosal ulcers, 6 (14.3%) low complement, and 8 (19.0%) increase DNA binding. Mean baseline HSS score 6.5, Physician's Global Assessment (PGA) score 1.31, and CLASI activity score 9.8. Ro or Sjögren's syndrome antibody (SSA) was positive in 17 (40.4%) of the subjects.
CC-220 demonstrated trends of improvement in the HSS, PGA, and CLASI scores. CC-220 was well tolerated. There were dose dependent effects upon lymphocyte and neutrophil counts observed. The most common adverse events were gastrointestinal disorders and infections, with the majority of these moderate or mild in severity.
Conclusions. CC-220 is a next generation immunomodulatory drug demonstrating trends in clinical and laboratory improvement in active SLE patients over 12 weeks of treatment with a safety and tolerability profile which supports further development for the treatment of SLE and other autoimmune diseases.

Key words: CC-220, Ikaros, cereblon

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THE 3RS STRATEGY: REDUCTION, REPLACEMENT AND REFINEMENT OF DRUG THERAPY IN A MONOCENTRIC SLE PATIENT COHORT

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Objective. Systemic Lupus Erythematosus (SLE) is treated according to severity and target organ involvement. Overall, hydroxychloroquine (HCQ) is of benefit but additional immunosuppressive therapy (IST) is often required (1). There are concerns about potential long-term consequences of IST. Risk of harm has been established to be low at long-term dosages of less or equal to 5mg prednisone equivalent/day (2), but is generally unknown for azathioprine (AZA), and mycophenolate mofetil (MMF), amongst others. The aim of this study was to implement universal HCQ therapy, reduce unnecessary steroid and other IST, while achieving disease remission without worsening organ damage.
Design and Method. We prospectively monitored and adjusted therapy in our group of SLE patients (100% fulfilment of ACR criteria with a diagnosis for at least one year). The study took place between January 2013 and March 2016. The demographic, clinical phenotypes, duration of disease, disease activity (quantified by SLEDAI), presence of organ damage (SLICC SDI score) and baseline therapies were recorded at the time the 3Rs strategy was implemented and sequentially alongside drug changes (introduction, removal, increase or reduction in dosages). Flares were considered according to standard definitions (3).
Results. At inclusion: 84 (94%) were women, 79 (89%) Caucasian, mean age and disease duration 47 and 14 y. The majority were in remission (75%). Caucasians were less represented amongst the patients with active disease (SLEDAI>2) which also included most of the patients that had nephritis together with neuropsychiatric manifestations. As regards therapy, after 3 years of follow-up, HCQ was maintained at 80% while GC, AZA and MMF use were reduced from 73, 35 and 10 to 49, 25 and 7%, respectively. In 14 of the 44 subjects that required GC, the daily dose was successfully reduced to a dose smaller or equal to 5 mg/day of prednisone equivalent. MMF discontinuation was mostly due to pregnancy planning (3/4). Discontinuation of AZA due to side effects was associated with flares (n=5/13) and occurred in patients with active disease. Flares, n=27 (30%), were mostly articular, occurred in younger patients, of less disease duration, with previous nephritis, with a higher SLEDAI at inclusion and were more frequent in those patients that discontinued AZA and MMF but not steroids. Belimumab was used successfully in 8 patients. At the end of study, the % of patients with a SLICC SDI score <1 and a SLEDAI<3 was similar.
Conclusions. Implementing IST reduction or discontinuation may be hampered by uncertainty about the risk of disease flare and organ damage. Our results demonstrate the 3R strategy can be safely followed in the clinical care of SLE patients.

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Key words: 3Rs strategy, therapy, flare

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RESETTING THE IMMUNE SYSTEM WITH IMMUNOABLATION AND HEMATOPOIETIC STEM CELL TRANSPLANTATION IS ASSOCIATED WITH A NORMALIZATION OF TYPE I INTERFERON (IFN) ACTIVITY IN SLE

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Objective. Our previous studies provided the proof-of-concept that depletion of the autoreactive immunologic memory by immunoablation followed by transplantation of autologous hematopoietic stem cells (ASCT) is associated with a "reset" of the immune system in systemic autoimmune diseases, such as SLE. Here, we aimed to analyze whether immune reset in SLE is associated with a normalization of type I interferon activity, a hallmark of SLE immunopathology.
Design and Method. Serum levels of IFN2a were investigated with the DELFIA assay (Miltenyi Biotec) before and after ASCT and Siglec-1 expression on $CD14^+$ monocytes (as IFN surrogate) analyzed using flow cytometry. In addition, the gene expression profile was analyzed with Microarray (Affymetrix) from FACS-sorted $CD14^+$ monocytes in SLE patients after HSCT, compared to those from SLE patients with active disease and healthy controls.
Results. Since 1998, ten patients with treatment-refractory SLE received a $CD34^+$-selected ASCT after immunoablation with antithymocyte-globulin and cyclophosphamide. Long-term remissions (SELENA-SLEDAI <=3) were achieved for up to 17 years after ASCT despite withdrawal of immunosuppressive therapy, while three patients suffered a relapse of SLE. Serum IFN2a levels significantly decreased from a median 43.1pg/ml at baseline to 3.01 pg/ml at 2 years after HSCT (p<0.001) and Siglec-1 expression on monocytes completely normalized in responding patients after ASCT and was only elevated in patients during viral infections and prior to SLE flares. Compared to patients with active SLE, the IFN signature probe-sets with a cut-off of fold change >=2 or <=2 in monocytes from ASCT-treated patients decreased down to 24% (77/320) and clustered with healthy controls, suggesting a normalization of type I IFN signature.
Conclusions. Resetting the immune system with ASCT is associated with a complete normalization of the IFN signature in SLE suggesting that up-regulation of IFN-related genes is not a predisposition but rather the consequence of chronic autoimmunity in SLE. Apparently, immunoablation resets the innate immune system into a self-tolerant state where even up-regulation of IFN during viral infections is not associated with reactivation of SLE.

Key words: stem cell transplantation, lupus, interferon acivity

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CORTICOSTEROIDS DOSE AFTER 6 MONTHS OF INDUCTION THERAPY IS ASSOCIATED WITH NON-RENAL ORGAN DAMAGE IN PATIENTS WITH LUPUS NEPHRITIS

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Objective. Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that can involve major organs, leading to significant morbidity and organ damage. Lupus nephritis (LN) is one of the most common and serious organ involvement and long-term corticosteroids, especially at high doses, used for its treatment can cause organ damage. We investigated the relationship between the corticosteroids dose after 6 months of induction therapy and organ damage.
Design and Method. We evaluated the patients enrolled in the Hanyang Bae Lupus Cohort after excluding those with pre-existing damage before induction therapy and incomplete information on renal biopsy pathologic findings. Patients with LN were all confirmed by renal biopsy and received induction therapy with either cyclophosphamide or mycophenolate mofetil and high-dose corticosteroids. Patients who tapered the prednisolones to less than or equal to 7.5 mg/d and those who failed to taper to 7.5 mg/d at 6 months after induction therapy were compared on demographic characteristics and SLE-related characteristics including the ACR classification criteria, disease activity (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and adjusted mean SLEDAI (AMS)), Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), LN class, and induction therapy regimen. Associations with organ damage were assessed by multivariate logistic regression adjusted for potential confounders.
Results. A total of 173 patients, including 35 patients with corticosteroids dose tapered to less than or equal to 7.5 mg/d at 6 months after induction and 138 patients who failed to taper to less than or equal to 7.5 mg/d were assessed. There were no significant differences in baseline demographics. SLEDAI at baseline was significantly higher in the patients who failed to taper (p<0.01). At 6 months, patients in the less than or equal to 7.5 mg/d group showed lower SLEDAI, AMS, and SDI scores. In univariate analysis, factors associated with development of damage were lupus anticoagulant (OR 2.07, 95% CI 1.05-4.07) and prednisolone greater than 7.5mg at 6 months (OR 3.20, 95% CI 1.17-8.78). They remained as independent risk factors in multivariate analysis (OR 2.18, 95% CI 1.07-4.45 and OR 3.92, 95% CI 1.27-12.15, respectively). When the damage was divided into renal and non-renal damage, only prednisolone greater than 7.5 mg/d at 6 months was associated with non-renal damage (OR 3.77, 95% CI 1.06-13.41) and there was no factor associated with renal damage.
Conclusions. Failing to taper corticosteroids less than or equal to 7.5 mg at 6 months of induction therapy is associated with non-renal organ damage in patients with lupus nephritis.

Key words: lupus nephritis, corticosteroids, damage

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LONG TERM EFFICACY AND SAFETY OF TACROLIMUS FOR PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Tacrolimus (TAC) has been evaluated as a strong immunosuppressive agent adapted for many transplantation. TAC had been adapted for rheumatoid arthritis and lupus nephritis since 2007 in Japan. Long-term efficacy and safety of TAC for patients with systemic lupus erythematosus (SLE) including lupus nephritis were evaluated in this study.
Design and Method. We picked up the SLE patients treated with TAC in our hospital started from 2007 to 2009. We checked retrospectively the reason of adding TAC, steroid dose, and the levels of complement, anti-DNA antibody, and SLEDAI (SLE disease activity index). We evaluated the persistence rate of TAC, efficacy for SLE including steroid sparing effect, safety, and adverse effects.
Results. We found 60 patients treated with TAC from 224 patients with SLE followed in our hospital since 2005. They were 8 males and 52 females, and their average age was 37.8±12.2 year-old. The reasons of adding TAC were mainly the difficulty to decrease steroid dose due to reasons as follows: elevation of anti-DNA antibody 31 cases (51.7%), hypocomplementemia 8 cases (13.3%), proteinuria 7 cases (11.7%), skin lesions 15 cases (25.0%), arthritis 2 cases (3.3%), relapse after delivery 1 case (1.7%), thrombocytopenia 2 cases (3.3%).
The persistence cases of TAC were 37 cases (61.7%). The reasons of cessation of TAC were change of the living place for 3 cases, stop to come to our hospital with own responsibility for 4 cases, change to belimumab as the clinical study for 2 cases, death for 6 cases, the adverse effects 3 cases, relapse for 4 cases, and the patients' will for 3 cases.
The sparing effect of steroid was observed that prednisolone 11.1±6.2 mg/day as initial dose could decrease to 6.8±3.2 mg/day as final dose.
Conclusions. We considered that TAC was very effective for the many clinical features of SLE including nephritis and was relatively administered in safe. Especially, TAC was most effective for severe skin lesions of SLE. Although all hydroxychlorquine, azathioprine, cyclophosphamide, and mycophenolate mofetil were not officially adapted for SLE in Japan in 2009, TAC was the most effective immunosuppressive agent for SLE in Japan at present.

Key words: tacrolimus, systemic lupus erythematosus, immunosuppressant

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FACTORS DETERMINING HYDROXYCHLOROQUINE SERUM LEVELS IN A COHORT OF CHINESE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To study the factors determining the hydroxychloroquine (HCQ) serum concentration in a cohort of Chinese patients with systemic lupus erythematosus (SLE).

Design and Method. Consecutive patients who fulfilled the ACR criteria for SLE and had received HCQ for >=6 months were studied. Patients were prescribed HCQ at fixed daily dosages of 400/300/200mg/day or less according to disease activity, organ manifestations and risk factors for HCQ toxicities. Serum samples were assayed for HCQ by an in-house technique using the tandem mass spectrometry (SPE-MS/MS). Factors affecting HCQ serum concentrations were studied by univariate and multivariate linear regression analyses.

Results. 276 SLE patients were studied (94% women; mean age 41.0±13.8 years; SLE duration 8.7±6.6 years). HCQ was primarily used for mucocutaneous or musculoskeletal manifestations, or both, in 73%, 78% and 93% of the patients, respectively. Patients were stratified into 3 groups: (1) Total non-compliance (HCQ level <10ng/ml); (2) Sub-therapeutic (10-500 ng/ml); and (3) Therapeutic (>=500 ng/ml). The proportion of patients with HCQ levels of <10, 10-500, >=500 ng/ml was 11%, 77% and 12%, respectively. Patients with total non-compliance to HCQ were more likely to be in clinical and serological remission when compared to the remaining patients (42% vs 24%; p=0.04). However, no difference in the clinical manifestations could be observed between these two groups of patients. After excluding totally non-compliant patients, the mean and median HCQ serum concentration of the remaining 245 patients was 300±87ng/ml and 276ng/ml (interquartile range 167-401), respectively. Univariate linear regression revealed that the prescribed HCQ dosage (beta 0.47; p<0.001) and the SLEDAI score at recruitment (beta 0.16; p=0.02) were the significant factors associated with the HCQ serum concentrations. Multivariate linear regression showed that the prescribed HCQ dosage (beta 0.50; p<0.001) and eGFR (beta -0.14; p=0.02) were independent factors associated with HCQ serum levels. Age, sex, BMI, smoking, SLEDAI score and concomitant prednisolone were not significantly associated with the HCQ serum concentrations.

Conclusions. Non-compliance and sub-therapeutic HCQ serum levels were frequent in our SLE patients. Patients with lower eGFR or receiving higher doses of HCQ were more likely to achieve higher HCQ serum concentrations. Monitoring of HCQ level and dosage adjustment may be helpful in reducing the risk of toxicities.

Key words: antimalarial, lupus, flare

P5:100

RITUXIMAB INDUCES SHORT-TERM IMPROVEMENT IN SEVERE DISSEMINATED DISCOID LUPUS ERYTHEMATOSUS LESIONS IN THE SETTING OF SYSTEMIC LUPUS ERYTHEMATOSUS ASSOCIATED WITH NEPHRITIS

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Objective. Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE). DLE lesions can occur in up to 28% of those with systemic lupus erythematosus (SLE), with variable associations with lupus nephritis (LN) reported. Overlapping immunopathological mechanisms in SLE and CLE are likely, however T-cell predominance and high $CD8^+$ staining in DLE suggest a less crucial role of B-cell mediated inflammation. Accordingly, the response of CCLE to B-cell depletion therapy has been mixed in the reports cases to date.

The purpose of this study was to describe the clinical and serological characteristics of a cohort of patients with DLE, particularly with regard Rituximab response and LN.

Design and Method. We reviewed 31 patients presenting to a tertiary referral center with histologically proven DLE. Localized DLE (LDLE) was defined as DLE lesions limited to the head and/or neck; DDLE was defined as lesions above and below the neck. SLE was diagnosed according to SLICC classification criteria. Objective disease severity was measured utilizing Cutaneous Lupus Area and Severity Index (CLASI) and mucocutaneous BILAG. Subjective disease impact was measured with Dermatology Life Quality Index (DLQI) scores.

Results. Twenty-two patients (71%) had LDLE and 9 (29%) had DDLE. Nine patients (2 with LDLE, 7 with DDLE) had skin lesions in the context of SLE; 4 had LN and 4 received Rituximab therapy (Table I).

Of those with LN, all had DDLE and 3 were treated with Rituximab. Mucocutaneous BILAG category was A for all those with LN, compared to category B or C for those without LN.

In total, 4 patients were treated with Rituximab; all had SLE (3 with LN) and pre-existing severe DDLE (pre-treatment CLASI activity scores 29, 16, 33, 22; pre-treatment mucocutaneous BILAG category A in three cases, B in one). Three patients initially responded at 1-month (CLASI activity scores decreased by >10 points in all; BILAG category C in two, B in one), only to flare back to baseline severity at 3-months in one and 6-months in two cases. DLQI scores were >15 pretreatment, <10 at time of response and >12 at 4-6 months. This was despite ongoing B-cell depletion, retained systemic response and ongoing concurrent immunosuppressive therapies. Serologically, all three initial responders were anti-dsDNA positive. The fourth patient, also with SLE associated DDLE (but anti-dsDNA negative and without LN) did not respond (Table 1).

Table. P5:100

Table 1. Demographic, clinical and serological characteristics of 9 patients with discoid lupus lesions in the setting of Rituximab treated SLE

Patient	Clinical Features	Immunological Features	Rituximab Treatment	Timing	CLASI	MUCOCUTANEOUS BILAG
No. 1 46yo F	- CCLE (DDLE) - Arthritis - Renal	- ANA 1:1280++ (coarse speckled) - anti-Sm, anti-dsDNA, anti-Ro - C3 and C4 low	Yes	Pre-treatment Response (1mth) Relapse (6mths)	29 17 31	A C A
No. 2 50yo F	- CCLE (DDLE) - Arthritis - Neurological - Renal	- ANA 1:640+ (fine speckled) - anti-dsDNA	Yes	Pre-treatment Response (1mth) Relapse (6mths)	33 19 31	A C A
No. 3 30yo F	- CCLE (DDLE) - Arthritis - Renal	- ANA 1:1280++ (fine speckled) - anti-dsDNA, anti-Ro - C3 and C4 low	Yes	Pre-treatment Response (1mth) Relapse (3mths)	22 11 21	A B A
No. 4 56yo F	- CCLE (DDLE) - Arthritis	- ANA 1:1280+++ (homogenous) - C4 low	Yes	Pre-treatment Response Relapse	16 Nil Nil	B Nil Nil
No. 5 36yo M	- CCLE (DDLE) - Arthritis - Serositis - Renal	- ANA 1:1280++ (homogenous) - anti-dsDNA - anti-Sm positive	No	Pre-treatment	Not available	A
No. 6 52yo F	- CCLE (DDLE) - Arthritis	- ANA 1:160+ (fine speckled) - C3 and C4 low	No	Pre-treatment	Not available	B
No. 7 40yo F	- CCLE (DDLE) - Non-scarring alopecia	- ANA 1:640+ (homogenous) - anti-dsDNA - anti-Sm	No	Pre-treatment	Not available	B
No. 8 41yo F	- CCLE (LDLE) - Arthritis	- ANA 1:160++ (fine speckled) - C4 low - Anti-phospholipid antibody	No	Pre-treatment	Not available	C
No. 9 51yo F	- CCLE (LDLE) - Leukopaenia	- ANA 1:1280++ (homogenous) - anti-dsDNA, anti-Ro - C4 low	No	Pre-treatment	Not available	B

Conclusions. This small series indicates initial but short-lived efficacy of Rituximab in severe DDLE associated with SLE, LN and anti-dsDNA positivity. Whilst initial response suggests B-cell related pathogenesis, early relapse despite ongoing B-cell depletion indicates independent T-cell pathways are significant in DDLE, even in the presence of SLE and autoantibodies. Characterizing variable immunopathogenic mechanisms within CCLE subtypes is vital to understanding observed inconsistent treatment responses.

Key words: cutaneous lupus erythematosus, discoid lupus erythematosus, ritixumab

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HYDROXYCHLOROQUINE PROTECTS AGAINST EARLY MYOCARDIAL DYSFUNCTION IN SLE

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Objective. Detrimental effects of HCQ on myocardium are well documented. Cardiac side effects are rare, however complete heart block and some cases of severe restrictive cardiomyopathy were described. Recent data suggest that HCQ may exhibit a protective effect against myocardial damage in SLE.
Purpose. To assess the prevalence of myocardial dysfunction in SLE and to establish whether HCQ has a protective effect on myocardial function.
Design and Method. Seventy-five SLE patients without clinical and ECG evidence of cardiac disease underwent transthoracic cardiac ultrasound using tissue Doppler imaging and speckle tracking echocardiography (STE). Patient characteristics and medication, cumulative organ damage (SDI damage index) and laboratory data were retrieved by medical chart review.
Results. Within the cohort 89.3%were female, with a mean (+SD) age of 43.2±12.5 years and a median (IQR) disease duration of 8.03 (6.3) years. Among the patients, 82.7% received longstanding treatment with HCQ. Patients on HCQ were younger (42.7 vs 48.5 years, p=0.03) and had a shorter disease duration (6.8 vs 9.4 years).
Within the non-HCQ group diastolic dysfunction of the left ventricle (69.2% vs 40.3%, p=0.05) anddecreased left ventricle deformation (endocardial longitudinal strain) by STE (-14.3% vs -18.7%, p=0.01) weresignificantly more frequent compared with the HCQ-group. By multivariate regression analysis the main independent determinants of systolic longitudinal dysfunction were HCQ as protective (beta=0.206) and antiphospholipid antibodies, SDI and prednisone as detrimental (beta=-0.343, -0.347 and -0.177, respectively). Diastolic dysfunction was negatively impacted by hypertension, SDI and disease duration (beta= 0.311, 0.312 and 0.257, respectively). Older age within the non-HCQ group was not a determinant for myocardial dysfunction.
Conclusions. Our data indicate that HCQ exhibits a significant protective effect against early myocardial dysfunction in SLE patients without evidence of cardiac disease.

Key words: myocardial dysfunction, hydroxychloroquine, echocardiography

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MEASUREMENT OF PLASMA MYCOPHENOLIC ACID IN PATIENTS WITH LUPUS NEPHRITIS AND INVESTIGATION OF THE NEED FOR DOSE INDIVIDUALIZATION

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Objective. Measurement of plasma Mycophenolic acid levels, development of a population pharmacokinetic (PopPK) model of Mycophenolic acid (MPA) after administration of Mycophenolate Mofetil (MMF) in patients with lupus nephritis (LN) and investigation of the need for dose individualization.
Design and Method. Pharmacokinetic data were obtained from 18 patients (mean age, weight and height 52 years, 64 kg and 164 cm, respectively) to whom 500, 1000 and 1500 mg of MMF were administrated. The MPA plasma concentration levels were measured before and 0.5, 2 and 4 h after the administration of MMF with a validated HPLC method. PopPK analysis was performed using NONMEM (version 7.3). Weight, age, sex, creatinine clearance (CLCR) were tested as potential covariates affecting the pharmacokinetic parameters. The final PopPK model was validated by non parametric bootstrap and visual predictive check (VPC).
Results. The final model was a one compartment model with first order absorption and additive error, with diagonal interindividual variability on all three parameters. No significant covariates were detected. Final model parameter values were CL=14.6 L*h-1, Vd=35.2 L and ka=4.14 with IIV 48.9%, 83.2% and 185%, respectively. Goodness of fit assessment using diagnostic plots such as depending variables (DV) vs PRED were considered reasonable. Internal validation by VPC revealed that the model describes well the data including the observed variability. Bootstrap analysis assured that model estimates were within the 95% confidence interval. The developed model was used to predict the individualized PK parameters needed for the calculation of the individualized dose for each patient in the study. Considering the same therapeutic range (TR) of AUC as for transplant patients, we calculated the % of patients falling within the TR equal to 28% (5 patients). From the 13 patients out of the TR, 5(38.5%), were marginally higher while the remaining 8(61.5%) were predicted as overdosed, probably needing lowering of the administered dose.
Conclusions. PopPK model for MPA after administration of MMF to patients with LN was developed. This model may serve as preliminary information for the Bayesian individualization of MPA pharmacokinetic parameters. More than 70% of the patients were predicted as overdosed indicating the need for dose individualization in this patient population.

Key words: mycophenolate mofetil, nephritis, pharmacokinetic

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IMMUNOSUPPRESSION WITH MYCOPHENOLIC ACID: SAFE AND EFFECTIVE INDUCTION AND MAINTENANCE TREATMENT FOR PROLIFERATIVE LUPUS NEPHRITIS PATIENTS

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Objective. To assess long-term efficacy of mycophenolic acid-either mycophenolate mofetil (MMF) or mycophenolic sodium (MFNa)-for induction and maintenance in patients with proliferative lupus nephritis (LN).
Design and Method. All 47 patients (41 female, 6 male) had proliferative LN:15 class III, 29 class IV and 3 mixed, with mean activity and chronicity indices 10±5 and 3±2 respectively. Mean patient age at SLE onset was 26±12 years while at the onset of nephritis it was 31±12 years. Median time from first SLE diagnosis until nephritis onset was 44 months (IR:4-110). Mean follow up of nephritis was 69±33 months. As induction therapy, 25 patients (53%) were treated with cyclophosphamide pulses and 22 (47%) received MPA--15(68%) of them MMF 2-3g/day and the remaining 7(32%) equivalent dose of MFNa plus steroids. For maintenance all received MPA for at least 2.5 years.
Results. Response to therapy was excellent. From the 47 patients, 41 (87%) achieved complete remission (CR) at a median of 7 months (IR:4-21). Almost half of them, 20 out of 47 (43%) had achieved CR already at the end of induction with 50% of them having received MPA. From the remaining 6/47 patients, 3 more achieved partial remission after 6 months (IR: 6-23) and 3 never achieved remission.
A total of 15 relapses occurred in 11 patients (23%) at 17 (IR:10-41) months: one while the patient was on full MPA dose, 5 during MPA tapering and 9 after treatment discontinuation. Therapy toxicity was minimal: five out of 15 patients on MMF (33%) had gastrointestinal symptoms. There were two episodes of severe infection and one episode of herpes zoster.
At the end of follow up, 16 out of 47 patients (34%) have successfully completed maintenance and 38(80%) are in complete remission. From the entire cohort, only one patient is dialysis dependent.
Conclusions. This single center study further confirms the excellent long-term results of MPA as induction and maintenance treatment in a large cohort of homogeniouslly treated, Caucasian patient population with active proliferative LN.

Key words: nephritis, mycophenolic acid, outcome

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COMBINATION THERAPY OF MYCOPHENOLATE MOFETIL AND CYCLOSPORINE A FOR INDUCTION TREATMENT OF REFRACTORY LUPUS NEPHRITIS: SUCCESSFUL TREATMENT OF DIFFICULT CASES

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Objective. To analyze efficacy and tolerability of multitarget immunosuppression with mycophenolate mofetil (MMF) and cyclosporine A (CsA) for induction treatment of lupus nephritis (LN) refractory to standard induction therapy (CYC and/or MMF).
Design and Method. We analyzed efficacy and tolerability of MMF+CsA rescue induction treatment for patients with LN (class III/IV/V, ISN/RPS 2003 classification) refractory to at least one standard regimen (CYC and/or MMF) for 6 months. All cases from a 400-patient prospective SLE cohort followed at a tertiary Lupus Clinic and treated between 2012 and 2015 are reported.
Results. Six patients with lupus nephritis (100% female, 100% Caucasian, age: 23-52 years) are reported. The LN was class IV in 3 cases, class V in 2 and class III in 1. Four patients had previously received i.v. pulse CYC and all 6 had received MMF as first or second choice. After failure of achieving response with previous regimes, CsA was added to MMF. An ACE inhibitor or ARB and prednisone were given with all regimens. Daily dose of MMF was 2-3 g and CsA was dosed up to 2.6-3.7mg/kg/day. Mean prednisone dosage was 17.5 mg/day at baseline and reduced to 6 mg/day after 6 months of MMF+CsA. At start of MMF+CsA regimen, mean proteinuria was 2407 mg/24h and reduced to 1484 mg/day and 544 mg/day after 3 and 6 months, respectively. Mean serum creatinine was 0.53 mg/dl at start of MMF+CsA and 0.68 mg/dl after 6 months. Four patients achieved complete renal remission, one patient had a 48.8% reduction in proteinuria and one failed to respond. The mean time to complete remission was 5 months. One patient stopped CsA after 36 months due to nausea and vomiting. No patients presented raised blood pressure or other adverse events with this rescue multitarget induction.
Conclusions. In this case series, combination of MMF and CsA was effective and well tolerated in most cases as a rescue induction treatment of class III/IV/V LN after failure of standard therapy. This option deserves consideration in such difficult cases with few available treatment choices.

Key words: lupus nephritis, refractory, multitarget induction therapy

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MEDICAL ADHERENCE OF PATIENTS WITH LUPUS ERYTHEMATOSUS IN GERMANY 2012 – RESULTS OF THE LULA COHORT STUDY

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Objective. Medical adherence is an important factor influencing therapeutic success. In the majority of patients the lack of adherence remains unrecognised and/or is misinterpreted as non- respectively not-adequate response. This study investigated the frequency and influencing factors of low resp. high adherence in German lupus patients.
Design and Method. The Lupus erythematosus (LE) long-term study (LuLa-Study), a longitudinal study of the German LE self-help community on a multitude of LE associated factors, is being conducted annually by means of a self-reported questionnaire since 2001. In 2012, we included questions concerning medical adherence (Morisky Medication Adherence Scale; MMAS-4) as well as a questionnaire to assess beliefs about medication prescribed (BMQ) and about the patients' health locus of control (HLoC).
Results. We received 579 questionnaires of whom 458 participants were eligible for analysis (81 were omitted due to not taking any lupus medication and 40 because of incomplete MMAS-4 questionnaires). 62.7% showed a high, 32.5% a moderate and 4.8% a low adherence.
In a multivariable logistic regression, use of azathioprine (OR: 1.85; 95% CI: 1.02, 3.34), glucocorticosteroids <7.5 mg (OR: 1.56; 95% CI: 0.97, 2.49), higher age (OR: 1.06; 95% CI: 1.03, 1.08) and external HLoC (powerful others) (OR: 1.15; 95% CI: 1.01, 1.30) were significant factors for lupus patients having a high adherence (MMAS-4 score = 4). Inclusion of a variable was assessed by the likelihood-ratio test (forward selection). The general perception of medication being harmful or addictive (OR: 0.89; 95% CI: 0.815, 0.97) and own income (OR: 0.73; 95% CI: 0.45, 1.19), suggestive of an employment, on the contrary proved to be prejudicial for adherence.
Conclusions. Our reported adherence rates in LE are consistent with those reported by others. Several factors affecting medical adherence in lupus patients are detected. Especially in employed younger patients, patients fearing the harmfulness of medication and those with a low external (powerful others) health locus of control, lower medical adherence needs to be considered. As the choice of the medical agent has an additional impact on patients' adherence provision of sufficient information and education addressing these potential obstacles might help to improve adherence and reach the best possible outcome.

Key words: medical adherence, systemic lupus erythematodes, self-reported

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CHARACTERIZATION OF THE DIFFERENT HUMAN INTERFERON-ALPHA SUBTYPES INVOLVED IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Preclinical data provide evidence that IFN-α plays an important role in the pathogenesis of SLE and suggest that inhibition of this cytokine is an attractive target for therapeutic intervention in this disease. IFN-α per se constitute a group of 12 different molecules (IFN-α1, IFN-α2, IFN-α4, IFN-α5, IFN-α6, IFN-α7, IFN-α8, IFN-α10, IFN-α13, IFN-α14, IFN-α16, IFN-α17, IFN-α21) encoded by 13 different intronless genes. These subtypes share a large degree of homology, but are still different from one another regarding their structures and biological properties. To date, the precise IFN-α subtypes involved in SLE are unknown. Even if neutralizing anti-IFN-α monoclonal antibodies (Mabs) have been selected given their high rate of cross-reactivity against the different molecules of IFN-α, they can only target a subset of the 13 subtypes. The objective of this study was to characterize the IFN-α subtypes produced *in vivo* in SLE patients.
Design and Method. SLE patients were eligible for the study if they 1/ fulfilled at least four of the 1997 ACR criteria for SLE, 2/ had a lupus flare, and 3/ had a serum level of IFN-α, assessed with a bioassay above 2 Units/ml. In order to characterize the different IFN-α subtypes we used gene subcloning and sequencing which is still considered to be the most reliable procedure for identifying individual IFN-α subtypes since the nucleotide differences between the genes encoding IFN-α subtypes is too small to discriminate between them by hybridisation with specific probes for Polymerase Chain Reaction or by specific ELISAs. The method consist in extracting mRNA from total blood samples, to eliminate DNA contamination with DNase, to transform RNA extract into cDNA and to amplify the 13 IFN-α subtypes by PCR, using a consensus oligonucleotide primer pair designed to amplify the coding sequences of all known IFN-α genes (panIFN-α PCR). The purified panIFN-α product is cloned using the TA cloning method. The DNA from randomly selected clones is sequenced using the Sanger method.
Results. 7 patients were included (6 women and 1 man). The median SLEDAI score (extrems) was 13 (8 – 19). The 7 patients had a severe lupus flare. The clinical signs of disease were: fever for 7 patients, mucocutaneous manifestations for 5, leucopenia for 4, glomerulonephritis for 3, serositis for 2 and arthritis for 1. The Farr assay was positive for 6 patients. C3 serum level was low for 6 patients. The frequencies of the different IFN-a subtypes performed on purified panIFN-a product is described in the Table).
Conclusions. The IFN-α subtype pattern showed an overrepresentation of the subtype 21 and to a lesser degree 4, 5, 8, 1/13 and 17. Several subtypes were weakly present or even absent: 2, 6 and 14. These results should help to improve the development of MAbs targeting IFN-α.

Key words: interferon alpha, biologics

Table (P5:106)

IFN-α subtype	Patient#3	Patient#4	Patient#6	Patient#11	Patient#13	Patient#22	Patient#15	mean	SD
Alpha 1 and 13	3.3	14.6	22.4	3.1	18.1	0.0	7.5	9.8	8.6
Alpha 2	5.3	7.8	3.0	2.3	5.2	4.0	13.0	5.8	3.7
Alpha 4	8.6	6.8	10.4	13.8	9.5	0.4	6.2	8.0	4.2
Alpha 5	15.2	12.6	10.4	21.5	2.6	1.2	1.2	9.3	7.9
Alpha 6	0.0	0.0	1.5	0.0	0.0	0.4	2.5	0.6	1.0
Alpha 7	18.5	3.9	7.5	20.0	1.7	0.8	10.6	9.0	7.8
Alpha 8	6.6	12.6	13.4	2.3	12.1	9.5	2.5	8.4	4.7
Alpha 10	7.9	6.8	4.5	0.8	6.9	9.1	8.1	6.3	2.8
Alpha 14	0.0	1.0	3.0	0.8	0.9	0.4	22.4	4.0	8.1
Alpha 16	3.3	10.7	7.5	0.8	10.3	0.4	2.5	5.1	4.4
Alpha 17	4.0	6.8	10.4	4.6	12.9	40.5	9.3	12.7	12.7
Alpha 21	27.2	16.5	6.0	30.0	19.8	33.3	14.3	21.0	9.7
Total	100	100	100	100	100	100	100	100	

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HOW FREQUENT IS REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS? REAL LIFE DATA FROM A MONOCENTRIC COHORT

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Objective. There is no generally accepted definition for remission of SLE. Recently an international expert panel met to achieve consensus, by drafting and testing potential definitions of remission in SLE.
Purpose: To evaluate what proportion of patients fullfills several potential definitions of disease remission as proposed by DORIS (Definitions Of Remission in SLE) consensus meeting, in a monocentric cohort of SLE patients.
Design and Method. This is a retrospective analysis of data prospectively collected in a longitudinal observational cohort of SLE patients established in our centre in 2011; patients fulfilling the 1997 ACR classification criteria who attended the last visit from January 2015 to April 2016 were enrolled in this study. Among patients regularly followed in our cohort, those with complete clinical and serological data available at last observation were included in this analysis. The DORIS definitions of remission LLDAS were applied to each patient during the study period.
Results. 141 patients were eligible for the study (97.1% females, mean age 44.99±15 years). The mean disease duration at enrolment was 15.5±9.7 years (range 1-42) and 42.5% of patients has accrued organ damage (SLICC/DI equal or greater than 1). One hundred and twelve patients (112/141) were on treatment for SLE (glucocorticoids and/or immunosuppressants and/or biologics), 29 patients were off treatment or were taking only antimalarial drugs.The frequency of remission according with the definitions proposed is reported in Table I.
Interestingly, high concordance rate was found among the definitions based on the global scores (SLEDAI, ECLAM) and the clinical definition. More stringent definitions of remission (no clinical and negative serology) were rarely reached in patients off treatment; while the same criteria were satisfied in a good proportion of patients (up to 24%) under treatment with GC and/or immunosuppresants. Interestingly, patients in clinical and serological remission off treatment tended to be younger with a shorter disease duration (p=0.06).

Table I.

Definition of remission	Off treatment (%)	On treatment (%)
cSLEDAI=0 and PGA<0.5	28 (20%)	60 (42.5%)
cSLEDAI=0 and PGA<0.5 +negative serology	13 (9.2%)	32 (22.7%)
cECLAM=0 and PGA<0.5	25 (17.7%)	49 (34.7%)
cECLAM=0 and PGA<0.5+ negative serology	10 (7%	28 (19.8%)
No symptoms of active SLE	28 (19.8%)	70 (49.6%)
No symptoms of active SLE + negative serology	13 (9.2%)	34 (24.1%)

Conclusions. In our cohort, a small percentage of patients fulfils the more stringent definitions of remission proposed by DORIS, especially if we consider patients off treatment. Remission on treatment appears a feasible goal in this real-world setting. Longitudinal analysis would be necessary to confirm whether patients with stable remission on treatment would have poorer clinical outcomes.

Key words: remission, systemic lupus erythematosus, DORIS

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SUCCESSFUL TREATMENT WITH BELIMUMAB AFTER INADEQUATE RESPONSE TO PREVIOUS THERAPEUTIC REGIMENS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. REAL LIFE EXPERIENCE

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Objective. Systemic lupus erythematosus (SLE) is characterized by variable clinical course. Nowadays, there are new drugs with a novel mechanism of action which are indicated for the treatment of patients with SLE. The aim was to describe the effect of belimumab in a cohort of SLE patients having had inadequate response to previous therapeutic regimens.
Design and Method. A cohort of five patients with SLE, 4 female and 1 male, aged 45, 49, 54, 68 and 36 years, respectively, is described. Belimumab was administered after inadequate response to treatment with corticosteroids, hydroxychloroquine, azathioprine, in one case mycophenolate mofetil, and in one case pulse cyclophosphamide. All patients had leucopenia, lymphopenia, skin involvement, positive anti-dsDNA antibodies, positive ANA and positive anti-Sm antibodies in two cases. In one case severe renal involvement was also present with membranoproliferative glomerulonephritis. In one case pulmonary involvement was present and in one case severe central nervous system involvement. All patients had fatique. In all patients 25(OH)D3 levels were measured.
Results. After belimumab treatment, fatique improved, skin manifestations improved impressively, lymphopenia, leucopenia and thrombocytopenia normalized and complement levels improved. Corticosteroid dosage was decreased in all cases. In 2 of the 5 SLE patients low 25(OH)D3 levels were detected.
Conclusions. Belimumab is a synthetic monoclonal antibody which inhibits B-cell activating factor (BAFF) indicated for the prevention and treatment of flares in SLE. Belimumab leads to clinical and laboratory improvement in SLE and a diminished need for corticosteroids. As, until very recently there was a paucity of medications for the treatment of SLE, belimumab is a long awaited addition in the armamentarium of rheumatologists for the treatment of systemic lupus erythematosus.

Key words: belimumab, remission, corticosteroids

P5:111

SYSTEMIC LUPUS ERYTHEMATOSUS RELATED-THROMBOCYTOPENIA SUCCESSFULLY TREATED WITH BELIMUMAB AFTER RITUXIMAB FAILURE

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Objective. Thrombocytopenia in patients with SLE show a wide range of clinical scenarios ranging from mild and asymptomatic, requiring observation only, to severe and immediately life-threatening, requiring aggressive immunological and/or surgical therapy. No randomised controlled clinical trials are available to guide therapy and maintenance schedules are still debate.
Design and Method. We describe a case of SLE-related thrombocytopenia treated with belimumab at the relapse after anti-CD20 therapy.
Results: A 27 years old woman suffering from SLE with skin, joint and haematological manifestations, low C3 and C4, anti-dsDNA and antiphospholipid antibody positivity presented a mild thrombocytopenia (111.000/uL). Cyclosporine 3 mg/kg/die was started but was soon reduced and then stopped for systemic arterial hypertension and unremitting headache. After 6 months platelet count dropped to 17.000/uL; prednisone 1 mg/kg/die was introduced with only transient improvement on platelet count and azathioprine was started without efficacy. Patient underwent infusional high dose steroids followed by rituximab 1 gram two weeks apart, obtaining a good clinical response but a relapse of severe thrombocytopenia at month +5 after rituximab therapy, while CD19+ cell count was still under 5 cells/ul. She developed also headache relapse, malar rash and cutaneous acral vasculitis and azathioprine was reintroduced; clinical picture furthermore worsened with neutropenia and pleuropericarditis. Methylprednisolone 1 g/day for three days and high-dose IVIG was given and belimumab 10 mg/kg was start soon after the 1^ IVIG cycle. Platelet count normalized soon after the 2^ IVIG cycle and a progressive global improvement was seen. IVIG were stopped after the III cycle and patient continued with belimumab, OHchloroquine and low dose steroids without need to reintroduce any DMARD. During a follow up of 24 months there was no relapse of thrombocytopenia nor skin and joint flares. Anti-dsDNA antibodies and C3 did not change significantly while C4 got back to normal. Last SLEDAI score is 4. B-cell count slightly increased during belimumab therapy.
Conclusions. Targeting B lymphocyte stimulator (BLyS) in SLE-associated thrombocytopenia may be a good option for the maintenance of response in the long-term, avoiding more problematic immunosuppressive agents in young patients. Also in SLE, as demonstrated in SS-associated cryoglobulinemic vasculitis, targeting local survival factors for B-cells might be crucial in order to maintain the lowest grade of disease activity.

Key words: thrombocytopenia, treatment, belimumab

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CONCEPT OF SELECTIVE SPHINGOSINE-1-PHOSPHATE RECEPTOR 1 (S1P1R) MODULATION IN AUTOIMMUNE DISEASES

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Objective. To review the concept, mode of action (MoA), available clinical data of oral S1P1R modulators and to assess their treatment potential in autoimmune diseases.
Design and Method. Review of published studies and data on file at Actelion Pharmaceuticals Ltd.
Results. Clinical efficacy in relapsing remitting multiple sclerosis (MS) of the non-selective S1PR modulator fingolimod suggests a potential role in the treatment of various autoimmune diseases. This class of compounds discriminates from prototypical immunosuppressive drugs by reversible sequestration of T and B cells in the lymphoid organs. Apart from MS and in line with preclinical models, recent clinical trials showed potential benefit in psoriasis [ponesimod, Vaclavkova 2014] and ulcerative colitis [ozanimod, Sandborn 2015].
Actelion clinical Phase II results in MS have shown a dose-dependent therapeutic effect of the selective S1P1R modulator ponesimod [Olson 2014]. Based on the clinical data a daily dose of 20 mg was selected for Phase III pivotal trials. A ponesimod Phase II open-label study investigates the pharmacokinetic (PK) - pharmacodynamic (PD) relationship and biological activity in chronic graft versus host disease. In parallel, the Actelion 2nd generation potent, oral, selective S1P1R modulator cenerimod is currently studied in generalized (focus: musculoskeletal and muco-cutaneous) systemic lupus erythematosus (SLE) patients with limited disease activity (SLEDAI-2K: 2 to 12). This Phase I/II multicenter, randomized, double-blind, placebo-controlled, 12 week treatment, dose-response study aims to explore the biological activity, safety, tolerability, and PK of cenerimod. First trial results are expected in 2017.
Conclusions. Several clinical studies test the concept of S1P1R modulation and are suggesting the potential clinical benefit for the treatment of various (auto-) immune-mediated disorders.

Key words: Sphingosine-1-phosphate (S1P), receptor modulator, autoimmune disease

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THE RITUXILUP PROTOCOL: A CASE REPORT OF INNOVATION AND THERAPEUTIC SUCCESS

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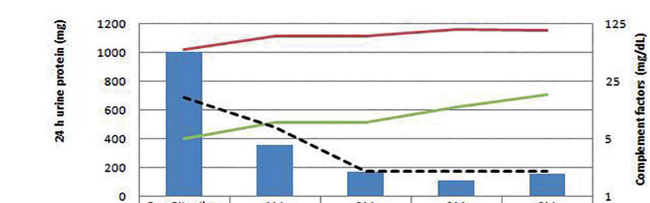
Objective. Lupus nephritis (LN) is a serious complication of Systemic Lupus Erythematosus (SLE), affecting up to 30-60% of patients. Approved regimens include a combination of glucocorticoid (GC) therapy and cytotoxic agents, usually mycophenolate mofetil (MMF), cyclophosphamide or azathioprine. Chronic GC use is associated with significant morbidity and mortality, providing a compelling need for the use of alternative therapies. LN has been successfully treated with the Rituxilup protocol (1).
Design and Method. We describe a prospectively documented case of LN treated with a GC free regimen.
Results. 16-years old female, diagnosed with SLE 3 years prior to admission in our Unit, on the basis of 5 SLICC criteria (alopecia, cutaneous lesions, arthritis, anti-nuclear antibodies, anti-dsDNA positivity and low complement). She had been previously treated with up to 30 mg/day of deflazacort and azathioprine, all of which were progressively discontinued due to lack of efficacy. When she was hospitalized, in July 2015, she was off medication and presented with widespread pruriginous and erythematous cutaneous lesions affecting approximately 80% of her body surface. Laboratory tests revealed leucopenia (3100 u/l), high anti-dsDNA titers (277 IU/mL by ELISA), complement consumption and proteinuria (1006 mg/24 h). We resumed hydroxychloroquine (400 mg/d), started angiotensin converting enzyme inhibitor and MMF while awaiting the outcome of renal biopsy. It showed active class V membranous glomerulonephritis with mild mesangial proliferation and parietal and interstitial granular deposits that stained positive for IgG, IgM, IgA, C4, C3, C1q and light chains (ISN/RPS). The patient was treated with rituximab (RTX) 1g preceded by methylprednisolone 500 mg, on day 1 and 15. Maintenance therapy with MMF (1g/day) was gradually increased 250 mg/week to 2 g/day. There was rapid resolution of the skin lesions, hair re-growth, well-being and sustained complete renal remission, maintained at 6 months, with progressive normalization of the leucocyte count, C3 and C4 (Fig. 1) and reduction of anti-dsDNA titers. Initial RTX resulted in complete B cell depletion with re-population (CD19+ B cell 6%) documented at 6 month post-treatment.



	Pre-Rituxilup	1M	2M	3M	6M
Proteinuria	1006	358	169	113	158
C3 (90-180)	61	89	89	106	104
C4 (10 – 40)	5	8	8	12	17
SELENA-SLEDAI	16	7	2	2	2

Conclusions. The Rituxilup protocol is based on the fact that in renal transplantation the use of depleting antibodies has allowed the safe introduction of steroid-free regimens. It consists of 2 doses of RTX (1 g) and methylprednisolone (500 mg) on days 1 and 15, and maintenance treatment with MMF. Despite the negative results of the trial with RTX in LN (2), several observational studies have demonstrated that RTX is well tolerated and achieves high remission rates in LN (3), as we describe in this case. We await the results of the ongoing randomized multicenter trial that will hopefully define the possibility of a steroid-free strategy for LN.

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Key words: lupus nephritis, rituxilup, remission

P5:114

TARGETING THE TYPE I INTERFERON SYSTEM IN SLE

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Design and Method. The type I interferon (IFN) system is our main defense against viral infections. This is achieved by inhibition of viral replication and stimulation of the innate and adaptive immune systems. Several observations suggest an important role for the type I IFN system in the etiopathogenesis of SLE, but also several other autoimmune diseases. Among these observations are development of SLE during treatment with IFN-α, an increase in the expression of type I IFN regulated genes (an IFN signature) in SLE patients, the existence of endogenous IFN inducers in SLE patients and a genetic association between SLE and gene variants within the type I IFN signaling pathway. Important type I IFN effects are maturation and differentiation of dendritic cells, activation of T and B cells with enhanced antibody production. Consequently, type I IFNs can act as an immune adjuvant and promote an autoimmune process, suggesting that inhibition of the type I IFN system could be beneficial in SLE. Many different therapeutic targets exist and a number of studies are in progress aiming to block, or down-regulate, the type I IFN system in SLE. Several studies with monoclonal anti-IFN-α antibodies have been reported, and a small study investigating vaccination with an interferon-α-kinoid against IFN-α has been published. Trials targeting the type I IFN receptor are under way, and preliminary data was recently reported with positive results. Other possibilities include elimination of the endogenous IFN inducers, inhibition of key molecules in the type I IFN signaling pathway or inhibition of plasmacytoid dendritic cells, the main type I IFN producer. The results so far show that it´s possible to partially suppress the IFN signature, improve several biomarkers and reduce clinical manifestations in SLE patients with moderate disease activity. No major safety problems have been observed, but complete inhibition of the type I IFN system will increase the risk for severe infections.
Results. The challenge for the future is to modulate the type I IFN system in SLE without interfering with the antiviral defense, and realize that different therapeutic targets may be appropriate in different disease subsets

Key words: Type I interferon, etiopathogenesis, treatment

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MAJOR IMPROVEMENT IN REFRACTORY SLE WITH BELIMUMAB

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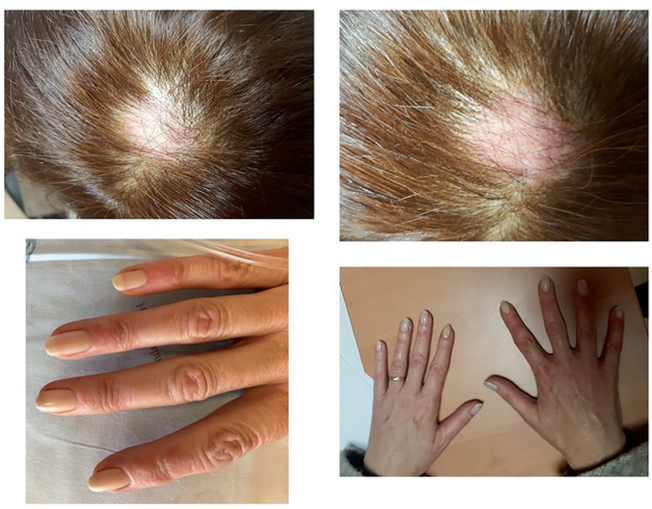
Objective. The treatment of Systemic Lupus Erythematosus (SLE) mostly relies on antimalarials, nonspecific immunosuppressants and variable doses of corticosteroids. However, some cases are difficult to manage being highly corticodependent and or unresponsive to immunosuppressive drugs, which will lead to significant morbidity in the long term. Belimumab is a novel biological therapy, SLE-specific, which acts targeting specific molecules in this disease pathway. It has shown promise as a steroid-sparing drug by reducing both the number of disease flares and corticosteroid usage.



Design and Method. The authors describe a case of refractory SLE treated with unacceptable chronic doses of steroids that responded to belimumab.
Results. A 55-year-old woman with a history of SLE diagnosed in 2001, presented in our clinic with fatigue, polyarthralgias, discoid lupus, alopecia, Raynaud's phenomenon and sicca symotoms. Anti-dsDNA was positive, although in a low level (<10 UI/mL). The disease was under reasonable control with hydroxicloroquine (HQC), azathioprine (AZA) and low dose deflazacorte (DFZ) until the end of 2011. Since then SLE manifestations have steadily worsened and monthly courses of intravenous immunoglobulin were tried over 4 years with some, but temporary success, and later discontinued due to intolerance (severe headaches). It was eventually resumed, but to improve tolerance and efficacy the subcutaneous formulation was successfully used, although it obliged to three hour infusions done 3 times per week and by mid-2015 the patient abandoned this regimen. The clinical exacerbation that followed and the need to increase systemic steroids (30mg of DFZ daily) compromised her self-esteem and quality of life. Skin manifestations were dominant with rash and severe alopecia patches. Fatigue was severe and she had incapacitating joint pain. Discrete hematological manifestations appeared and serological profile mirrored the high activity of the disease with high anti-dsDNA (281 UI/mL) and low C3 (0.88gr/L) levels. Belimumab was started in September 2015 at a 10mg/kg monthly regimen. With four infusions there was a mild clinical and a strong serological response: anti-dsDNA titers were negative, and both C3 and C4 levels were normal. By the 7th month, our most recent follow-up, a marked improvement was observed: she felt better with no joint pain or fatigue. Skin lesions improved, although not alopecia. No relapse was observed while tapering down the steroids, and the patient is currently on 7.5mg of DFZ daily. Concurrently she is on AZA 100mg and HQC. No side effects related to the biological drug were noticed.
Conclusions. Despite the short follow up, this case demonstrates the success of belimumab as an adjuvant therapy in refractory SLE, allowing a significant reduction of corticosteroids without clinical or serological relapse. As our understanding about SLE molecular mechanisms advances, one should expect more targeted therapies and safer options to control the disease, without the well-known morbidity of chronic steroids use.

Key words: belimumab, steroid-sparing drug, refractory SLE

Poster session 6: Organ involvement, flare, remission and damage

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PREDICTION OF CHRONIC DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS USING NEURAL NETWORKS

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Objective. The increased survival in patients affected by Systemic Lupus Erythematosus (SLE) implies the development of chronic damage: treatment adverse events, disease activity and comorbidities seem to be the major risk factors. The prevention of damage is a major goal in the SLE patients management. In the studies published so far, up to 50% of patients develop damage after 10 years from the diagnosis. In the present study, we aimed at predicting chronic damage in a large monocentric SLE cohort by using neural networks.
Design and Method. We enrolled 400 consecutive patients affected by SLE (ACR 1997 revised criteria; M/F 29/371; mean age ± SD 47.5±14.3 years; mean disease duration ± SD 106.8±98.4 months) referring to an out-patient Lupus Clinic. Chronic damage was determined by using the SLICC/ACR Damage Index (SDI). Predictors of patients at increased risk of damage development were identified and validated using recurrent neural networks, a prediction model that automatically learns from data using sequential information. In our setting, we have used, as input to the neural network, the set of available clinical and laboratory features (27) of the patients observed in the sequential visits performed during the follow-up. The binary output of the neural network (for the classification task) indicates whether or not a chronic damage will be detected at the next visit of a given patient. Since the data do not have balanced class distribution, we used the AUC to evaluate the predictive ability of the learning model. Finally, we applied a feature selection technique in order to identify the most relevant clinical features in the predictive modelling problem.
Results. During the disease history, 180 patients (45%) developed chronic damage: musculo-skeletal resulted the most frequent involved organ system (15.5%). Concerning the neural network, 40 patients developing chronic damage during the follow-up were considered as cases and 100 patients never developing damage and with at least five visits were considered as controls. The available data were randomly splitted into eight different training and test sets preserving the percentage of positive and negative examples. The recurrent neural network was trained by a standard stochastic gradient descent method. The overall AUC obtained for the eight folds was 0.74. Moreover, the most relevant features in the predictive model are the following: age, concomitant anti-phospholipid syndrome and neurological manifestations.
Conclusions. In the present study, for the first time we applied neural networks in order to identify a prediction model for chronic damage in SLE patients. The evaluation of a wide cohort allows the identification of a model with a good predictive ability. Moreover, the identification of concomitant anti-phospholipid syndrome and neurological manifestations as most relevant features in the predictive model confirms the role of anti-phospholipid antibodies in the damage development.

Key words: chronic damage, predictive model, neural network

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CLINICAL FEATURES AND PROGNOSES OF ACUTE TRANSVERSE MYELITIS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Acute transverse myelitis (ATM) is a rare but severe complication of systemic lupus erythematosus (SLE). This study evaluated the clinical factors related to outcome in patients with SLE-associated ATM.
Design and Method. The medical records of patients diagnosed with SLE-associated ATM between January 1995 and January 2015 were retrospectively reviewed. The clinical characteristics, laboratory values including cerebrospinal fluid (CSF), and spine magnetic resonance imaging (MRI) images were obtained. The severity of neurologic involvement was assessed according to the American Spinal Injury Association scale. The patients were divided into two groups based on improvement of neurological deficits after treatment: favorable response and unfavorable response groups. During follow-up, the recurrence of ATM was also analyzed.
Results. ATM was identified in 16 patients with SLE. All of the patients were treated with high doses of methylprednisolone (over 1mg/kg daily). Additionally, 14 patients (87.5%) and 9 patients (56.3%) were treated with methylprednisolone pulse therapy and cyclophosphamide pulse therapy, respectively. Although 12 patients (75%) recovered (favorable response group), 4 (25%) had persistent neurologic deficits (unfavorable response group) after treatment. Compared to the favorable response group, significantly higher Safety of Estrogens in Lupus: Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index scores (16.6±11.1 vs. 27.0±2.4; p=0.042) and lower complement levels (C3 88.3±33.6 mg/dL vs. 43.3±4.6 mg/dL; p=0.020, C4 16.1±6.2 mg/dL vs. 9.2±1.1 mg/dL; p=0.030) were found in the unfavorable response group. Among the 12 favorable response patients, 5 (41.7%) experienced recurrence of ATM during the follow-up period. Patients (n=5) who experienced relapse had a shorter duration of high-dose corticosteroid treatment (13.2 days vs. 32.9 days; p=0.01) compared to patients who did not relapse.
Conclusions. Higher disease activity in SLE might be associated with the poor outcome of ATM. In addition, prolonged high-dose corticosteroid therapy might be helpful for preventing the recurrence of ATM.

Table. Clinical characteristics at presentation according to the treatment responses of SLE-associated ATM.

	Unfavorable response group (n=4)	Favorable response group (n=12)	p value
Gender, female (%)	4 (100)	11 (91.7)	1.000
Age (year)	38.3±15.8	37.0±14.9	0.953
SLE duration (months)	82.8±92.8	22.0±46.6	0.058
SELENA-SELDAI	27.0±2.4	16.6±11.1	0.042
Initial severe myelitis[a]	4 (100)	3 (25)	0.019
C3 (mg/dL)	43.3±4.6	88.3±33.6	0.020
C4 (mg/dL)	9.2±1.1	16.1±6.2	0.030
CH50 (mg/dL)	11.2±3.83	40.6±19.6	0.013
High Anti-ds DNA Ab[b]	4 (100)	3 (25)	0.019
NMO	0	2 (16.7)	1.000
ESR (mm/hr)	63.8±41.9	39.6±38.3	0.316
CRP) mg/dL)	1.88±1.38	2.53±5.25	0.316
CSF-WBC (mm^3)	608.8±730.3	15.3±32.9	0.148
CSF-Glucose (mg/dl)	65.3±67.6	57.7±19.5	0.710
CSF-Protein (mg/dl)	131.1±135.1	84.3±78.3	0.604
Longitudinal myelitis	3 (75)	8 (66.7)	1.000
Foley catheter, n (%)	4 (100)	6 (50)	0.234
Death[c]	2 (50)	0 (0)	0.050
Treatment			
HD steroid duration, days	21.8±10.8	24.7±13.6	0.770
Cyclophosphamide, n (%)	1 (25)	7 (58.3)	0.569
Rituximab, n (&)	1 (25)	0 (0)	0.250

[a]Initial ASIA grade: A,B,C.
[b]High Anti-ds DNA Ab: serum anti-dsDNA Ab >20IU/ml.
cCauses of ddeath: infection (osteomyelitis and bacteremia) (n=1), heart failure (n=1).

Key words: transverse myelitis

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RESORBTION OF IMMUNE DEPOSITS IN MEMBRANOUS LUPUS NEPHRITIS FOLLOWING TREATMENT – A TOOL TO EVALUATE RESPONSE?

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Objective. The evaluation of treatment response in membranous lupus nephritis (MLN) is difficult and is mainly based on reduction of proteinuria. Studies on repeat renal biopsies in MLN are limited. In a small previous study on MLN-patients treated with rituximab (RTX), electron-microscopy (EM) revealed resorption of subepithelial immune complex (IC) deposits in repeated renal biopsies in parallel with clinical response. It is not known whether the resorption phenomena observed may be useful for treatment evaluation or has impact on long-term prognosis.
We studied if EM from repeated renal biopsies could be useful for evaluation of treatment response in MLN and if the amount of ICs or resorption phenomena differs after RTX vs. conventional immunosuppressive treatment. We also studied if EM-findings could predict long-term prognosis.

Table I. Electron-microscophy findings before and after treatment, grading according to immune complex deposit score.

Patient	Treatment	Subepithelial ICs (before/after)	Resorption phenomena (before/after)	Podocyte fusion (before/after
Pat 1	AZA	2/3	1/0	1/3
Pat 2	AZA	1/1	0/1	1/1
Pat 3	AZA	3/1	0/1	1/3
Pat 4	CYC	1/1	1/2	2/2
Pat 5	CYC	2/3	0/0	2/3
Pat 6	CYC	2/1	2/2	2/1
Pat 7	CYC	3/3	0/1	3/2
Pat 8	CYC	3/1	2/3	3/2
Pat 9	CYC	1/1	1/1	3/3
Pat 10	CYC	3/3	0/0	3/3
Pat 11	MMF	1/1	1/1	1/0
Pat 12	MMF	1/2	2/0	1/1
Pat 13	MMF	2/2	0/0	3/2
Pat 14	MMF	1/1	1/1	2/2
Pat 15	MMF	1/2	0/1	3/3
Pat 15*	RTX	2/2	1/2	3/2
Pat 16	RTX	2/1	1/1	2/3
Pat 17	RTX	1/1	2/3	2/1
Pat 18	RTX	3/1	1/2	3/3
Pat 19	RTX	1/2	1/2	3/2

* in patient number 15, three biopsies were performed. ICs: immune complexes; AZA: azathioprine; CYC: cyclophosphamide; MMF: mycophenolate mophetile; RTX: rituximab.

Design and Method. Nineteen patients with pure MLN in whom renal biopsies were performed before and after immunosuppressive treatment were included in the study. Five of the patients had been treated with RTX and the rest received conventional treatment. One patient underwent a third biopsy after RTX-treatment and thus, altogether 39 renal biopsies were available for evaluation (Table I).
Clinical and routine laboratory data were collected at both biopsy occasions. The biopsies were graded according to the ISN/RPS-classification. Electron micrographs of renal tissue were scored semi-quantitatively (using an arbitrary scale 0-3) for the amount of subepithelial ICs, resorption of IC-deposits and podocyte fusion. Long-term renal outcome was determined after a median of five years.
Results. All patients had active MLN at baseline (ISN-class V). Follow-up biopsies showed class II (n=1), III C (n=1), III/V (n=1) and V (n=17). All patients treated with RTX had decreased or unchanged amount of supepithelial ICs. No biopsies from the RTX group had an increase of ICs, whereas in the conventional treatment group, 6/15 had an increase (p=0.09). Of RTX-treated patients, 4/5 (80%) had increased resorption phenomena vs. 5/15 (33%) in the conventional treatment group (p=0.07). At baseline, the amount of subepithelial ICs correlated to albuminuria (r=0.52, p<0.05). No other correlations between EM-findings and routine laboratory variables were found, and there was no association between the amount of ICs, resorption phenomena or podocyte fusion with long-term renal outcome.
Conclusions. We report a clear trend towards a decreased amount of ICs, and increased resorption phenomena in the glomerular basal membrane, after treatment with RTX vs. conventional therapy. Although not statistically significant, this is of interest since recommendations for both treatment and evaluation of MLN are limited. Further studies on a larger group of patients are needed to address the question if EM-findings may have impact on the prognosis.

Key words: membranous lupus nephritis, electron microscopy, rituximab

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EFFECTS OF RISK FACTORS FOR METABOLIC SYNDROME AND THE COMPONENTS OF METABOLIC SYNDROME ON THE QUALITY OF LIFE OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A STRUCTURAL EQUATION MODELING APPROACH

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Objective. This study assessed 1) relationships among risk factors for metabolic syndrome (MS), components of MS, and health related quality of life (HRQOL), and 2) the effects of these variables on HRQOL in a hypothesized causal model using structural equation modeling (SEM) in Korean patients with systemic lupus erythematosus (SLE).
Design and Method. Of the 505 patients with SLE enrolled in the Korean Lupus Network (KORNET registry), we investigated 244 patients with sufficient data to assess the components of metabolic syndrome at the time of cohort entry. We evaluated the education, income, corticosteroid dose, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physicians Global Assessment (PGA), depression, components of metabolic syndrome, and HRQOL at the time of cohort entry. SEM was used to test the structural relationships of the model using AMOS software ver. 23.
Results. The 244 patients had an average age of 40.7±11.8 years and included 228 (93.4%) women. The SEM results supported the good fit of the model (χ2=71.629, df=56, p=0.078, RMSEA 0.034, CFI 0.972). The final model showed that higher education and income had a direct negative effect on MS and higher disease activity had a positive indirect effect on MS as mediated by the corticosteroid dose. Higher education and income had indirect effects on HRQOL, and higher disease activity had a direct negative effect on HRQOL. MS had no direct impact on HRQOL, but an indirect negative impact on HRQOL as mediated by depression.
Conclusions. In our causal model, risk factors for MS were related to MS, directly and indirectly. MS had a negative indirect impact on HRQOL as mediated by depression. Therefore, clinicians should consider socioeconomic status, medication, and depression and try to modify the disease activity and metabolic syndrome, to improve the HRQOL of SLE patients.

Key words: metabolic syndrome, quality of life, risk factors

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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) RESPONDER INDEX [SRI(4)] RESPONSE IS ASSOCIATED WITH GLOBAL BENEFIT IN PATIENTS WITH MODERATE TO SEVERE SLE

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Objective. *Post-hoc* analysis of two Phase III studies of belimumab (1) showed that an SRI(4) response is associated with clinically meaningful benefits, irrespective of treatment assignment. Confirmation of these findings in independent cohorts will enhance the acceptance of SRI(4) as a measure of clinically meaningful improvement. This analysis assessed global clinical benefit represented by an SRI(4) response.
Design and Method. Changes from baseline in clinical, laboratory, and patient-reported outcome measures at Day 365 were compared between SRI (4) responders (n=396) and non-responders (n=340) in the combined dataset of two Phase II studies evaluating sifalimumab and anifrolumab in moderate to severe SLE.
Results. Baseline demographics were similar between the studies. At Day 365, a greater percentage of responders than non-responders had ≥7-point reduction in SLE Disease Activity Index 2000 (SLEDAI-2K) and had their oral corticosteroid dose reduced to ≤7.5 mg/day (Table). Responders also had greater percentage changes from baseline in clinical SLEDAI scores, and greater improvements in Physician's Global Assessment (PGA) score and number of organ domains with SLEDAI-2K improvement. British Isles Lupus Assessment Group (BILAG) "A" or "2B" flare rates were lower in SRI(4) responders. Among patients with ≥8 swollen and ≥8 tender joints at baseline, a larger percentage of responders had ≥50% improvement in swollen and tender joint counts. In patients with baseline Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥10, more responders had ≥50% improvement. In patients with abnormal baseline serological parameters, responders had greater improvements in anti–double-stranded DNA concentrations; however, differences in complement C3 and C4 concentrations were not significant. Responders also had greater improvements in patient-reported outcomes: percentage change from baseline in Patient Global Assessment, and absolute change in Short Form 36 Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scores.
Conclusions. SRI(4) response in patients with moderate to severe SLE was associated with broad improvements in clinical, laboratory, and patient-reported outcomes, confirming previous findings suggesting SRI(4) response is associated with global clinically important benefits.

Reference

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Key words: anifrolumab, sifalimumab, efficacy

P6:121

CLINICAL PARAMETERS RELATED WITH ORGAN DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS: DATA FROM KOREAN LUPUS NETWORK (KORNET) REGISTRY

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Objective. The aim of this study was to identify whether demographic and clinical parameters are related to organ damage in patients with systemic lupus erythematosus (SLE).
Design and Method. A total of 502 SLE patients enrolled in the KORean lupus Network (KORNET) were consecutively recruited from four university-based medical centers (Daegu, Seoul, and Gwangju) in Korea. Data included demographics, age-adjusted Charlson comorbidity index (CCIa), disease activity indexes, the SLICC/ACR damage index (SDI), the 36-item Short Form Health Survey (SF-36) score, and the Beck depression inventory (BDI) score.
Results. Of the total patients, 21.1% (n=106) experienced organ damage (SDI >= 1). Multivariate regression analysis revealed that SDI was related to age, disease duration, SLEDAI, CCIa, and corticosteroid therapy (p=0.028, p=0.015, p=0.034, p<0.001, and p=0.015, respectively). There were significant differences in BDI, mental component score of the SF-36, SLEDAI, CCIa, CRP, and mean dose of corticosteroid between non-damage (SDI=0) and damage (SDI >= 1) groups. The presence of damage to at least one organ in patients with SLE was found to be closely related with higher CCIa, higher SLEDAI, and mean dose of corticosteroid (odds ratio [OR]=1.884, 95% CI 1.372 – 2.586, p<0.001; OR=1.114, 95% CI 1.041 – 1.192, p=0.002; OR=1.036, 95% CI 1.004 – 1.068, p=0.026) in binary logistic regression analysis.
Conclusions. This study suggests that organ damage as assessed by the SDI in Korean SLE patients is related to comorbidities, disease activity, and corticosteroid exposure.

Key words: SLICC/ACR damage index, comorbidity, SLEDAI

Table (P6:120). Changes from baseline in outcome measures compared between SRI(4) responders and non-responders at Day 365.

	Responders (n=396)	Non-responders (n=340)	*p*-Value[a]
Day 365			
SLEDAI-2K ≥7 point reduction, n (%)[b]	223/360 (61.9)	1/306 (0.3)	<0.001
Reduction of oral corticosteroid dose to ≤7.5 mg/day, n (%)[c]	76/235 (32.3)	10/188 (5.3)	<0.001
Percentage change in Clinical SLEDAI, mean (SD)	-80.5 (21.5)	-14.4 (29.1)	<0.001
Percentage change in PGA, mean (SD)	-71.7 (26.6)	-13.6 (27.7)	<0.001
Organ domains with improvement on SLEDAI-2K, mean (SD)	2.19 (0.73)	0.29 (0.59)	<0.001
BILAG "A" or "2B" flares, n (%)[d]	20 (5.1)	73/333 (21.9)	<0.001
≥50% improvement in joint counts, n (%)[e]	136/143 (95.1)	26/143 (18.2)	<0.001
≥50% improvement in CLASI, n (%)[f]	90/104 (86.5)	19/100 (19.0)	<0.001
Percent change in serology, mean (SD) [n][g]			
anti-dsDNA	-13.5 (69.8) [200]	6.0 (90.8) [112]	0.051
Complement C3	11.4 (25.4) [148]	13.0 (29.1) [77]	0.676
Complement C4	31.7 (92.5) [86]	36.6 (68.0) [50]	0.728
Change in SF-36, mean (SD)			
PCS	6.3 (9.5)	1.3 (5.8)	<0.001
MCS	4.3 (11.1)	-0.1 (6.9)	<0.001
Vitality	5.2 (9.3)	0.1 (5.5)	<0.001
FACIT– Fatigue, mean (SD)	6.5 (11.3)	0.7 (7.4)	<0.001

**P*-value is from 2-sample t-test for continuous variables and chi-square test for categorical variables; [b]In patients with SLEDAI-2K ≥7 at baseline; [c]Reduction of OCS dose at Day 365 to ≤7.5 mg/day in patients who were receiving ≥10 mg/day at baseline; [d]BILAG "A" or "2B" flares at any time during the study up to Day 365; [e]≥50% decrease in swollen and tender joint count from baseline in patients with ≥8 swollen and ≥8 tender joints at baseline; [f]≥50% improvement in CLASI from baseline in patients with CLASI ≥10 at baseline; [g]Improvement of serological parameters in patients with abnormal baseline values. Anti-dsDNA: anti-double-stranded DNA; BILAG: British Isles Lupus Assessment Group; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; Clinical SLEDAI: at least a 4-point reduction in clinical components (no laboratory components) of Systemic Lupus Erythematosus Disease Activity; FACIT: Functional Assessment of Chronic Illness Therapy; MCS: Mental Component Summary; PCS: Physical Component Summary; PGA: Physician's Global Assessment; SD: standard deviation; SF-36: Short Form 36 Health Survey; SLE: Systemic Lupus Erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SRI: Systemic Lupus Erythematosus Responder Index.

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WHAT IF "NEUROLUPUS" ISN'T SYSTEMIC LUPUS ERYTHEMATOSUS AFTER ALL? ANTIPHOSPHOLIPID ANTIBODIES INCREASE NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTI-SMITH ANTIBODIES MIGHT PROTECT FROM IT

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Objective. Neuropsychiatric involvement (NPSLE) represents a heavy burden for Systemic Lupus Erythematosus (SLE) patients and their management. Several studies have been clarifying the role of antiphospholipid (APL) antibodies in NPSLE, disclosing the possibility of redefining some NPSLE syndromes as non-thrombotic Antiphospholipid Syndrome (APS) manifestations. We studied the interaction between APL antibodies and the presence of NPSLE and between the latter and the occurrence of non-thrombotic non-NPSLE defining manifestations; we also studied the eventual associations between said variables and immunological markers.
Design and Method. Currently adult SLE patients were selected from our unit cohort. Exclusion criteria: age inferior to 18yo, APS with thrombotic or obstetric events. Clinical and immunological data was collected from the charts. Data analysis was performed using SPSS software.
Results. From the 198 patient population, 90.4% were women and 9.6% were men. The mean age at SLE diagnosis was 31.95 yo (9-65), with a mean follow-up time of 14.82 years (1-39). A total of 32 patients (16.9%) had NPSLE, mostly focal syndromes (a total of 13.8%). Out of the 198 patients, 81 (40.9%) tested positive for APL antibodies according to the Sydney APS classification criteria. Even without clinical APS, NPSLE occurred more frequently when APL antibodies were positive (25.3% vs. 11.0%)(Chi2=6.64, p=0.010; OR=2.74, 95%IC[1.25-6.01]), and occurred less frequently when anti-Smith antibodies were positive (5.1% vs. 19,6%)(Chi2=4,67, p=0.031; OR=0.22, 95%IC[0.05-0.97]). NPSLE was more prevalent when non-thrombotic non-NPSLE defining manifestations were present (balance problems or vertigo, avascular hip necrosis or frequent fractures, sleep disturbances, self-reported not confirmed memory or attention deficits, mood or behavioural abnormalities) (43.8% vs 14.0%) (Chi2=8.33, p=0.004; OR=4.79, 95%IC[1.58-14.55]). No other antibody had a significant association with NPSLE involvement or with APL antibodies positivity.
Conclusions. Our results meet the current hypothesis that NPSLE is more linked with APL than with SLE itself and that this should be kept in mind in the approach of SLE patients. The fact that anti-Smith antibodies seem to be protective against NPSLE might reinforce the possibility of a different disease pathway, as has been reported by several others authors. If, in fact, these nosologic processes are due to undiagnosed or unclassified APS, this might imply the need for a more inclusive APS definition, with more sensitive diagnostic criteria.

Key words: neuropsychiatric SLE, systemic lupus erythematosus, antiphospholipid antibodies

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APPLYING LUPUS LOW DISEASE ACTIVITY STATE DEFINITION TO A COHORT OF PORTUGUESE LUPUS PATIENTS

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Objective. A definition of Lupus Low Disease Activity State (LLDAS) was very recently proposed. LLDAS is defined by: (1) SLEDAI 2K score <= 4, with no activity in major organ systems; (2) no new lupus disease activity compared with previous assessment; (3) a SELENA SLEDAI physician global assessment (PGA) (scale 0-3) <= 1; (4) a current prednisolone (or equivalent) daily dose <= 7,5mg; and (5) well tolerated stable maintenance doses of immunosuppressive drugs and approved biological agents. Objective of this study was to assess the rate of achievement of LLDAS in SLE patients from a tertiary care Lupus Clinic.
Design and Method. Consecutive Patients with SLE, fulfilling the SLICC'12 classification criteria, from a single tertiary lupus clinic were included in this cross-sectional study. Achievement of LLDAS was determined for each patient, at time of last visit. Reasons for non-achievement of LLDAS were recorded.
Results. We included 285 SLE patients (85.3% female; median age of SLE diagnostic - 34±14 years; median SLE duration – 14±9.6 years). From these patients, 89.1% were on LLDAS. Within the patients who did not reach LLDAS: 26 patients presented a SLEDAI score >4, in which 9 exhibit activity in major organ systems (renal involvement being the most prevalent), 14 were on treatment with a prednisolone dose >7.5mg daily and 2 presented a PGA >1.
Conclusions. The LLDAS state can be achieved by most patients followed in tertiary Lupus Clinics. Prospective studies are needed to determine if the LLDAS can be maintained over time.

Key words: lupus, low disease activity state, Portuguese cohort

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JUVENILE-ONSET LUPUS NEPHRITIS: INVESTIGATING THE ROLE OF THE GLOMERULAR ENDOTHELIAL CELLS IN NOVEL URINE BIOMARKER PRODUCTION

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Objective. Juvenile Systemic Lupus Erythematosus (JSLE) is a rare autoimmune disease that can affect many organ systems. Approximately 80% of children with JSLE suffer from chronic renal inflammation, known as lupus nephritis (LN). One of the most common clinical manifestations of LN is proteinuria due to impaired function of the renal glomerulus. Previous research has identified several candidate novel urinary biomarkers which are significantly elevated in the urine of JSLE patients with LN and include proteins of both renal and extrarenal origin such as monocyte chemoattractant protein-1 (MCP-1), neutrophil gelatinase-associated lipocalin (NGAL), alpha-1-acid glycoprotein (AGP), transferrin (TF), caeruloplasmin (CP), lipocalin-type prostaglandin-D2 synthase (L-PGDS) and vascular cell adhesion molecule-1 (VCAM-1). Our study objectives were to investigate whether the glomerular endothelial cells (GEnCs), which are necessary for urine production, can produce these biomarkers and how potential biomarker expression could be altered in LN, allowing for effective monitoring of renal disease.
Design and Method. Conditionally immortalized human GEnCs (ciGEnCs) were treated for 48 hours with 5% sera from patients with active LN (renal BILAG: A,B), patients with inactive LN (renal BILAG: D,E) and age- and sex-matched healthy controls. ciGEnCs in culture medium with 5% FBS were used as negative controls. ciGEnCs were also stimulated with 10ng/ml interferon alpha. After 48 hours, culture media were collected and total RNA was isolated. Real time PCR for all biomarkers and ELISAs for MCP-1, AGP and VCAM-1 were performed to determine mRNA and protein levels.
Results. MCP1, AGP, TF, LPGDS and VCAM1 mRNAs were expressed by all treatment groups and by negative controls, although there were no statistically significant differences in expression as analysed by qPCR. There was no detectable expression of NGAL and CP mRNA. MCP1, AGP and VCAM1 protein levels were significantly higher (p<0.0001) in ciGEnCs treated with sera from active and inactive LN patients and healthy controls but not in negative controls, or IFNα treated ciGEnCs. Active disease patients demonstrated increased AGP levels (1052 pg/ml; 1022-1121, p<0.05) compared to inactive disease (1011 pg/ml; 969.2-1053, p<0.05) and healthy controls (998 pg/ml; 954.9-1037, p<0.05).
Conclusions. The ciGEnCs can express MCP-1, TF, AGP, L-PGDS and VCAM-1. Human serum can induce the production of higher MCP-1, AGP and VCAM-1 proteins in both health and disease. The fact that there are not significant differences in mRNA and protein amounts for MCP-1, TF, L-PGDS and VCAM-1 suggests that GEnCs may not be the primary source of these urinary biomarkers or their production might be secondary to other contributors to renal inflammation in LN. Furthermore, other renal cells could be activated to produce higher amounts of MCP-1, TF, L-PGDS and VCAM-1 in active LN. AGP could be an important indicator of active LN and local kidney involvement in JSLE.

Key words: kidney, lupus, nephritis

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MRI-BASED CONNECTOMICS AS A TOOL TO EXPLORE NEUROLOGICAL INVOLVEMENT IN SLE

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Objective. Pathogenic mechanisms and specific clinical/radiological features of neurological involvement in patients with Systemic Lupus Erythematosus (SLE) have been only partially elucidated. The absence of tools to explore functional and anatomical networks that enable communication between distant regions of the brain might have restricted our insight on the events associated to SLE in patients with or without overt neurological manifestations of the disease (NP-SLE). Advanced methods of acquisition and analysis of MRI modalities, such as graph-analysis of functional and structural images (i.e., connectomics), open the possibility of mapping the connectivity across the entire brain. We relied on this approach to identify whether modifications of network topological organisation in the brain might occur in SLE patients and miht be associated to the clinical and biological features of the disease.
Design and Method. We have assessed, using resting-state (RS) functional MRI (fMRI), intrinsic functional connectivity (FC) and functional network connectivity (FNC) of brain, large-scale neuronal networks from 31 consecutive patients with SLE, classified or not as having neurological involvement, and 30 matched healthy controls. Independent component analysis was used to analyze RS fMRI data. Intrinsic FC of each cluster of each RS network (RSN) was compared between controls and patients (analysis of variance adjusted for age, gender, and gray matter volume). The FNC toolbox was used to assess interactions among RSNs. Neurological examination, psychological tests and rheumatologic assessment including SLEDAI, ECLAM and BILAG measurement were performed in parallel.
Results. Altered executive functions seem to be more evident in SLE patients and NPSLE patients in particular. No obvious relationship was found with treatment status or other confounders. Association analysis between specific MRI alterations and clinical/immunological features is ongoing.
Conclusions. Preliminary data suggest that MRI-based connectomics might represent a powerful and informative tool for NPSLE evaluation and might yield novel clues for a better understanding of the specific features of brain involvement in SLE even in patients without clinically apaprent neurological involvement. Further studies are necessary to verify this contention.

Key words: neuropsychiatric lupus, connectomics, magnetic resonance

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ASSESSMENT OF MICROVASCULAR DAMAGE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS – CAPILLAROSCOPIC EXAMINATION

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Objective. Nailfold capillaroscopy (NVC) is an imaging technique, noninvasive, inexpensive, easy to repeat, which has an important role in assessing microcirculation *in vivo*. Systemic lupus erythematosus (SLE), a multisystem autoimmune disease, has been described a wide array of vascular manifestation due to inflammatory and thrombotic lesions, occurring during clinical active disease
Objective: The purpose of this study was to evaluate the practical utility of NVC in patients with SLE, and define changes in the distribution and morphology of nailfold capillary density at these patients
Design and Method. The study included 97 patients with SLE diagnosed in according to ACR 1997 criteria. Changes nailfold capillaries were evaluated by VideoCap 3.0 magnification 200x. Capillaroscopic examinations were performed at fingers II - V on both hands in all patients. The finding classifications capillaroscopy was made in according to Maricq criteria. It was evaluated risk factors for vasculopathy - hypertension, smoking, sex, age, cholesterol, mellitus diabetes, drugs treatments, etc. Disease activity was assesed by SLEDAI index.
Results. All the patients were female, mean age 43,14±10,40SD (years), mean disease duration of 9,05±5, 21 (years). No change has been observed at capillaraoscopic exam in 17 patients without Raynaud´s phenomenon (RP), and 19 patients without RP showed minimal differences changes. Statistically significant changes were found in patients with or without RP who smoked (p 0.05), have a long duration of disease (p<0.0016), or have a disease activity score (SLEDAI) greater than 8, have positive antibodies and vascular manifestation as skin vasculopathy or cardiopulmonary involvements. Morphological changes at these patients were extended loops, dilated, microhaemorrages, moderate loss of capillaries and tortuous capillaries.
Conclusions. The nailfold capillaroscopic examinations in SLE patients, does not reveal a unique typical pattern, but a great variety of non specific changes can be observed at patients with skin involvment and disease activity and disease duration.

Key words: nailfold capillaroscopy, systemic lupus erytematosus, vasculopathy.

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BONE MINERAL DENSITY AND FRACTURE RISK IN A COHORT OF SYSTEMIC LUPUS ERYTHEMATOSUS WOMEN

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Objective. Emerging evidence has indicated that systemic lupus erythematosus (SLE) is associated with low bone mineral density (BMD) and osteoporosis (OP), with a special emphasis on disease activity and glucocorticoid use. However, the risk of developing osteoporotic fractures (OF) has not been extensively investigated.
We aimed to evaluate the prevalence and risk factors for low BMD and OF in SLE and to identify possible predictive factors for BMD loss.
Design and Method. Prospective observational study in consecutive SLE women (fulfilling either 1987 ACR or new SLICC/ ACR 2012 classification criteria) aiming to assess secondary OP. Controls were age-matched healthy women, addressed in the outpatient clinic with the suspicion of OP.
Classical risk factors for low BMD and fracture were evaluated in both study groups, while specific data including disease activity and damage, visceral involvement, autoantibody profile, glucocorticoid (GC) use, serum PTH and 25 (OH) vitamin D status only in SLE group.
BMD was systematically assessed at lumbar spine and femoral neck by DEXA (Medix 90) yearly, occurrence of fracture collected over 3 years, with a subsequent estimation of 10-year fracture risk by using the FRAX tool with the Romanian population reference. Reduced BMD and OP were defined according to the World Health Organization.
Statistical analysis (univariate, multivariate was done in SPSS, p<0.05.
Results. Among 85 SLE (mean age 45.7+12.9 years, mean disease duration 7.4+5.2 years) up to one third had low BMD, up to 15% OP and 1 out of 4 SLE developed OF over the follow-up, particularly in active SLE (p<0.05); conversely, only 11.76% present with BMD loss in the control group, with about 5% OF over time (p<0.05). Statistical significant differences in BMD between group (SLE vs healthy women) analysis for any site (p<0.05) were reported, with lower BMD in SLE, typically during disease flare and chronic renal involvement as well as with chronic GC administration. The mean 10-year risk of developing a major OF and a femoral neck fracture was higher in the SLE group (p<0.05). No specific information about PTH profile among SLE developing OP as compared to those with normal BMD, while significant impaired vitamin D levels.
Multivariate analysis (ANOVA) recognized a number of clinically relevant predictors for low BMD in SLE (p<0.05) including classical (familial OP history, age, menopause) and SLE-related factors (disease duration, fatigue, organ involvement such as renal impairment and neuropsychiatric complication) SLE activity and cumulative dose of GC).
Conclusions. SLE women are at risk to develop low BMD and OF as compared to healthy age-matched controls, particularly if cumulative risk factors such as age, SLE duration, disease activity and damage, and glucocorticoid use. Routine DEXA and risk factors for OP should be assessed in SLE.

Key words: systemic lupus erythematosus, osteoporosis, fracture risk

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SYSTEMIC LUPUS ERYTHEMATOSUS ACTIVITY IS ASSOCIATED WITH OXIDATIVE STRESS WITHOUT ANY IMPAIRMENT IN THE PLASMA ANTIOXIDANT CAPACITY

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Objective. Systemic lupus erythematosus (SLE) is the human autoimmune prototype disease. Oxidative stress (OS) is deeply involved in the SLE organ's damage during the active periods.
Design and Method. Sixteen SLE patients, divided according to their disease activity, were analyzed for their OS balances by the plasma malondialdehyde (MDA) and the plasma antioxidant capacity (PAC) by ORAC (Oxygen Reactive Antioxidant Capacity).
Results. While the active SLE group had significant higher levels of MDA compared to the group B (m1= 666.8± 60.2 vs. m2=532.2±40.3 MFI; p=0.01), it had no decreases in the PAC (p=0.21). Discussion: Our data concord with several previous reports that have demonstrated that SLE flares are strongly associated with OS. Our findings of the absence of PAC abnormality in the active SLE are explained by the fact that this first barrier against OS is rarely saturated, and constitute an additional confirmation that the impairment in the antioxidant defenses in SLE concerns more likely the second and/or the third barriers of these defenses; which are the enzymatic defenses and the complement factor H that neutralizes MDA.
Conclusions. SLE is an OS disorder without impairment in the first antioxidant barrier which makes questionable the antioxidant supplementation as a therapeutic approach.

Key words: oxidativee stress, active SLE, antioxidant defenses

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TO INVESTIGATE CAUSES FOR ADMISSIONS AND OUTCOMES IN HOSPITALISED SLE PATIENTS ADMITTED TO A TERTIARY HOSPITAL IN SOUTH AFRICA

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Objective. Main causes for admissions and outcomes in hospitalised SLE patients.
Design and Method. Patients and methods: Prospective observational study of SLE patients admitted over 12 months from February 2012 to January 2013. Patients older than 18 years fulfilling the 1997 ACR classification for SLE were included. Elective admissions for renal biopsy were excluded. Patient demographics, clinical and laboratory data, drug therapy, co-morbidities and outcomes were recorded.
Results. Of 86 admissions in 60 consecutive patients, most patients were female (92.7%) and Black (85.0%). Mean age at hospitalization was 34.6 years. Mean hospital stay was 15.1 days. 39(65. %) patients had nephritis and 8(13.3%) were HIV positive.
Newly diagnosed SLE accounted for 21 (35.3%) of the 86 admissions, with lupus nephritis being the most common diagnosis (45%). 42 patients were admitted once, 12 twice and 4 thrice and two pts were admitted on four occasions. Overall, the mean admission SELENA-SLEDAI score was 8 and the SLICC score was 0.94.
To determine the major cause of admission, we used the following categories 1) active SLE alone, 2) active SLE and infection, 3) infection, 4) thrombosis and 5) other. Active SLE accounted for 40 (46.5%) of admissions. Of these admissions 22 were for active lupus alone and 18 for flare and infection. Although multiple organ systems were frequently involved in admissions for active lupus, we classified such as admissions by the organ system most responsible for the admission. Nephritis (17) was the most common cause of flare.
Other medical and surgical causes accounted for 22 (25.6%) and infections accounted for 20 (23.3)% of the admissions. Most of the infections were bacterial. 8 patients had TB, 5 of whom had extra-pulmonary TB. Active SLE and flare accounted for 18(20.9%) of admissions and 4(5%) patients were admitted with thrombosis (2 MI, 1 PE, 1 CVA).
Eleven (18.3%) patients required haemodialysis and a further 9 (15 %) patients died. Main causes of death were multi-factorial in 5, cardiac 1, intracranial bleed 1 and unknown 1. Nosocomial sepsis occurred in 6/9 (66.7%) deaths.

Table I. Primary cause for admission.

	n (%)
Active SLE	22 (25.6%)
Active SLE and infection	18 (20.9%)
Infection	20 (23.3%)
Thrombosis	4 (4.7%)
Other medical and surgical	22 (25.6%)

Table II. Predominant organ involved in active SLE.

	n=40
Renal	17
Musculoskeletal	4
Neurologic	5
Mucocutaneous	3
Haematologic	4
Cardiopulmonary	2
Vasculitis	1
Multisystem flare	4

Conclusions. Active lupus, particularly lupus nephritis, was a major reason for admission in both newly diagnosed and known SLE patients, followed by admissions for other medical and surgical causes. Almost a third of patients were admitted on multiple occasions. Newly diagnosed SLE accounted for a small proportion of admissions, nephritis was commonly present. SLE hospitalization is associated with a high mortality. Nosocomial sepsis was a contributing factor in two thirds of the patients who died.

Key words: SLE, hospitalisations, outcomes

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MULTIPLE AUTOIMMUNE SYNDROME MIGHT PROTECT FROM SJOGREN'S SYNDROME-SPECIFIC ORGAN INVOLVEMENT – A CLINICAL, IMMUNOLOGICAL AND GENETIC ANALYSIS

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Objective. Several authors have described the genetic clustering between autoimmune diseases (AIDs) in Multiple Autoimmune Syndrome (MAS), but there are no sufficient published data to support differences in clinical and immunological features. Doctors empirically hypothesize that organ involvement in MAS patients is different from that of patients with only one of its diseases. We aimed to study if such differences exist and if MAS with Sjogren's syndrome (SjS) would protect from severe organ involvement in SjS alone, based on clinical, immunological and genetic data (namely in HLA and PTPN22).
Design and Method. Adult SjS patients were selected from our unit cohort. MAS was assumed when there were three or more autoimmune diseases. Exclusion criteria: having only two AIDs or undetermined diagnosis. Clinical and immunological data were collected from the charts. HLA-DRB1 was genotyped by PCR-SSP methodology; genotyping of PTPN22 rs2476601 polymorphisms was performed by TaqMan Real Time PCR. Data was analysed with SPSS software.
Results. 97 SjS patients were studied (92.8% women and 7.2% men); 42.7% had only SjS (monoautoimmunity subgroup) and 57.3% had SjS plus 2 or more other AIDs (MAS subgroup). The mean age at SjS diagnosis was 45.72 yo and mean follow-up time of 7.27 years. Clinical differences between the subgroups: parotid enlargement was significantly more frequent in the monoautoimmunity subgroup (OR=0.04 95%IC[0.005-0.313]); Raynaud's phenomenon was significantly more frequent in the MAS subgroup (OR=4.67 95%IC[1.91-11.39]). Immunological differences: rheumatoid factor was significantly more frequent in the monoautoimmunity subgroup (OR=0.397, 95%IC[0.167-0.945]). After correcting for

confounding factors, there were no other clinical or immunological differences between the subgroups.
HLA-DRB1*03 was more frequent in the study group, compared to the general population. HLA-DRB1*07 was significantly less frequent in the patients (both subgroups) with Raynaud's phenomenon (OR=0.16 95%IC[0.03-0.83]).
No differences were found between the mono and MAS subgroups regarding HLA-DRB1 or PTPN22.
Conclusions. HLA-DRB1*03 was confirmed in this study as a susceptibility allele for Sjögren syndrome. HLA-DRB1*07 seems to have, in both mono and MAS subgroups, a protective effect against Raynaud's phenomenon. Raynaud's phenomenon occurred proportionally more in MAS, probably due to its transversality in AIDs.
In our study, the higher prevalence of parotid enlargement and rheumatoid factor in SjS without other AIDs ("primary SjS") might postulate that, in MAS ("secondary SjS"), the scattering of the immune system could result in less significant SjS-specific organ involvement.

Key words: Sjögren syndrome, multiple autoimmune syndrome, genetic risk factors

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FULL HOUSE IMMUNOFLUORESCENCE PATTERN NEPHROPATHY: IS IT ALWAYS LUPUS NEPHRITIS?

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Objective. Describe a clinical case of Full house immunofluorescence nephropathy and literature review.
Design and Method. Case presentation. A 25 year-old woman without relevant medical history was admitted for nephrotic syndrome with proteinuria estimated at 4.35g/g creatinine, hypoalbuminemia (15 g/L) and normal renal function (serum creatinine 0.84 mg/dl). Urinary sediment was bland. Autoimmune tests (ANA, ENA, ANCA, complement) were negative as well as anti-phospholipid and anti-PLA2R antibodies. A renal biopsy was compatible with minimal change disease on light microscopic examination with normal glomeruli, tubulo-interstitium and vessels. However, immunofluorescence showed a full house pattern with intense mesangial and subendothelial depositions of C3 and C1q as well as all immunoglobulin classes. Electron microscopy showed mesangial and subendothelial dense immune-deposits. The patient was initially treated with oral corticosteroids (1mg/kg/day) but Mycophenolate Mofetil (MMF) (3g/day) and Plaquenil (400 mg/day) were added because of insufficient therapeutic response and histological features compatible with lupus nephritis. Over the following six months, the patient preserved a normal renal function while proteinuria progressively decreased from 12 to about 1 g/g creatinine.
Results. Discussion. Full house immunofluorescence staining pattern occurs most commonly in lupus nephritis but it has also been reported in broad spectrum of glomerular diseases like IgA nephropathy, membranous GN, type I membrano-proliferative GN, C1q nephropathy and post infectious GN. Our case extends this spectrum by a disease presentation suggestive of minimal change disease in an adult, with rapid onset nephrotic syndrome and completely normal light microscopy. Reported cases have in general been treated with immunosuppressive regimens similar to those proposed for overt lupus nephritis. Our patient showed no reduction in proteinuria after two weeks of monotherapy with high dose steroids and slowly progressive reduction of proteinuria over a 6 months period after adding MMF, underlining the need for intensive immunosuppression. The available literature suggests that 10-15% of patients with full house nephropathy subsequently develop overt Lupus. Patients should therefore be screened for the appearance of biological and clinical markers of Lupus in the long term.
Conclusions. Conclusion. Our case illustrates the difficult differential diagnosis and therapy of glomerular disease with full house immunofluorescence pattern in the absence of any other clinical manifestation or serological marker of Lupus.

Key words: lupus nephrits, full house immunofluorescence, nephrotic syndrome

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WHEN THE EYES DON'T SEE: A RARE PRESENTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

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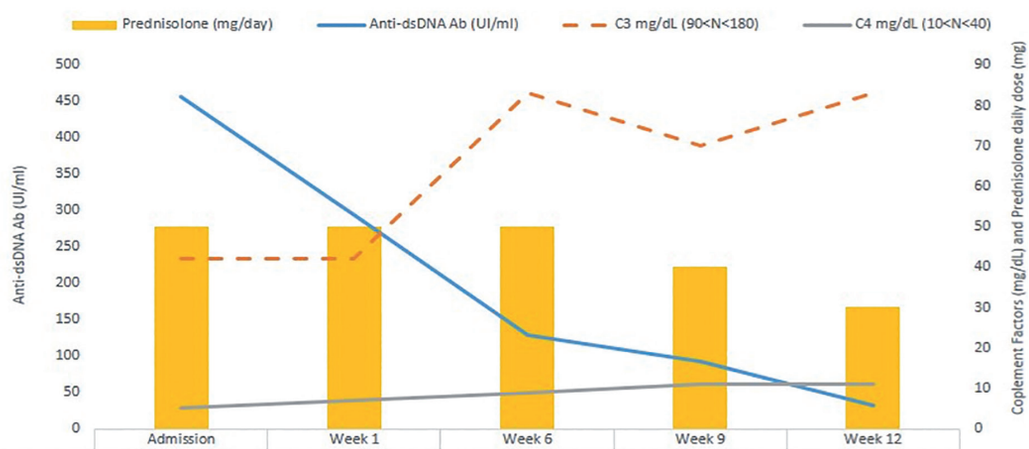
Objective. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a variety of presenting features. Current classifying systems adopted by the ACR and the SLICC comprise immunological and clinical criteria. Neither include eye involvement as a condition defining SLE although it is well known that ocular manifestations affect one-third of patients with SLE and may be the presenting feature of the disease (1).
Design and Method. The authors describe a prospectively documented case of lupus retinopathy as the initial feature of SLE.
Results: A previously healthy 23-years old Caucasian woman on oral contraception was admitted in December 2015 complaining of a two week history of fever, oral ulceration, polyarthralgia (knees and small joints of the hands) with morning stiffness of one hour and a three kilogram weight loss. Soon after admission she complained of blurred vision. Physical examination failed to show any abnormalities except for fundoscopy which revealed bilateral papillary oedema, cotton

Figure. P6:135

Figure 1. Follow-up: prednisolone dose, anti-dsDNA antibodies, C3 and C4



	Admission	Week 1	Week 6	Week 9	Week 12
Prednisolone (mg/day)	50	50	50	40	30
Anti-dsDNA Ab (UI/ml)	455,7	295	129,3	91,6	31,5
C3 mg/dL (90<N<180)	42	42	83	70	83
C4 mg/dL (10<N<40)	5	7	9	11	11

wool exudates and retinal vascular tortuosity. Visual acuity was 4/10 bilaterally. Blood tests documented a normocytic and normochromic anemia (hemoglobin 7.5g/dL), leucopenia (leucocytes 1100/µL); neutropenia (640/µL); total lymphopenia (370/µL); $CD4^+$ T cells 107/µL, ESR 96 mm/h, low C3 and C4, ANA 1/640 and anti-dsDNA antibody 455 UI/mL (positive >100), creatinine 0,52 mg/dL and a protein/creatinine ratio of 514mg/g with an otherwise inactive urinary sediment. Triple antiphospholipid antibody screen was negative. There was no evidence of HIV, CMV or EBV infection. Ophthalmological tests (OCT testing, retinography, angiography) revealed bilateral and symmetrical changes with marked neurosensory retinal oedema and haemorrhages, confirming the abnormalities found on fundoscopy. Cerebral MRI revealed no abnormality. She was treated with prednisolone 1mg/kg/day (50 mg/day) with marked improvement in visual acuity after two weeks (10/10 bilateral), full resolution of symptoms and proteinuria, sustained in time along with a marked decrease in the DNA titre and a rise in complement components (Figure 1). This was accompanied by an increase in the leucocyte count to 1290/µL and a normalized $CD4^+$ T cell count (550/µL). Thiopurine methyltransferase activity was normal. Azathioprine 50 mg/day was started and over the next 5 months prednisolone was progressively reduced to 15 mg/day. Small cotton wool exudates are still present and have, so far, precluded hydroxychloroquine therapy.

Conclusions. Lupus retinopathy occurs in about 10% of patients (2), although its presentation as an initial manifestation is rare. Ocular manifestations in SLE are associated with significant morbidity, needing a prompt diagnosis and treatment and are a marker of systemic disease activity (3). The diagnosis of SLE is classically supported by restricted clinical and immunological domains. We believe the ophthalmological manifestations in our report represent an unmet need in current SLE diagnostic criteria.

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Key words: Systemic lupus erythematosus, retinopathy, dagnostic criteria

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PLATELET TO LYMPHOCYTE RATIO AND NEUTROPHIL TO LYMPHOCYTE RATIO IN LUPUS NEPHRITIS PATIENTS

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Objective. The aim of this study was to evaluate the potential of platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) in lupus nephritis (LN) patients and explore their clinical significance.

Design and Method. A retrospective study involving 268 LN patients and 120 healthy controls was performed. All clinical characteristics of the LN patients were extracted from their medical records. NLR, PLR, mean platelet volume (MPV), and red cell width distribution (RDW) between LN patients and healthy controls were compared, and correlations between these indexes and clinical characteristics were analyzed. Proteinuria was also collected and defined as a protein/creatinine ratio>0,2.

Results. NLR, PLR, MPV, and RDW were significantly higher in LN patients than in the control group. NLR was positively correlated with C-reactive protein (CRP) (p<0,01), SLE Disease Activity Index (SLEDAI) scores (p<0,01) and protein/creatinine ratio (p<0,01). PLR was positively correlated with SLEDAI scores (p<0,01) and proteinuria (p<0,01). C-reactive protein values also correlated with PLR, MPV, and RDW, but the correlation was not statistically significant. NLR level of 1,98 was determined as predictive cut-off value of SLEDAI (sensitivity 76,4%, specificity 79,2%, AUC=0,84). Multiple regression analysis suggested that NLR was independently associated with SLE disease activity.

Conclusions. Our results suggest that NLR, PLR, and MPV may be used as easily available additional biomarkers in screening the Systemic lupus erythematosus population and could reflect inflammatory response and disease activity in LN patients.

Key words: lupus nephritis, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio.

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THE PREDICTIVE VALUE OF PHYSIOLOGICAL SCORES AND SPECIFIC INDICES FOR PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ADMITTED TO AN INTENSIVE CARE UNIT

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Objective. Patients with Systemic Lupus Erythematosus (SLE) requiring admission to an Intensive Care Unit (ICU) have a mortality of around 51%. The Logistic Organ Dysfunction (LOD) score is a physiological measure of severity, predicting hospital outcome. The SLEDAI (SLE Disease Activity Index) Measures SLE activity and the SLICC (Systemic Lupus International Collaborating Clinics) Index measures organ damage in SLE patients. There are few comparisons of these indices in predicting outcome for SLE patients in the literature.

Design and Method. A retrospective review of the hospital records of patients with SLE admitted to the Respiratory ICU at Groote Schuur Hospital (GSH) over a two-year period was undertaken. Data was collected for the calculation of the LOD, SLEDAI, and SLICC indices. Demographic features such as age, sex, disease duration and treatment at the time of admission were recorded. Patients who survived the ICU admission were compared with patients who died; in order to ascertain which indices best predicted a favourable outcome.

Results. Fifty-three patients with SLE admitted to ICU were identified. Only 48 of these could be analysed because the records of 5 patients could not be traced. The cohort was made up of 87.5% females, with a mean age of 33 (SD 11) years compared with males who were aged 41 (SD 10) years. The disease duration at the time of admission was 54.7 (SD 86.4) months. The overall mortality was 67%. The optimal SLEDAI score for predicting survival was 17, showing a sensitivity of 65.5%, specificity of 73.7%, positive predictive value of 79% and negative predictive value of 58.3%. The area under the ROC curve was 0.719.

Conclusions. SLE patients admitted to ICU have a high overall mortality of 67%. The SLEDAI was the best determinant of survival. The LOD and SLICC indices were not significantly different between patients who survived and those who died.

Key words: survival, ICU, predictors

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TRANSVERSE MYELITIS: A NEUROPSYCHIATRIC MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS VERSUS NEUROMYELITIS OPTICA

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Objective. Neuromyelitis optica (NMO) is a demyelinating autoimmune disorder characterized by optic neuritis, transverse myelitis and aquaporin-4 antibody seropositivity. The NMO disease spectrum includes Devic's syndrome and longitudinal myelitis in the setting of autoimmune diseases such as SLE and Sjögren's syndrome 1.

Design and Method. We report a series of three cases of transverse myelitis referred to our tertiary lupus clinic for the treatment and evaluation of presumed neuropsychiatric systemic lupus erythematosus (SLE).

Results. Two patients presented with upper and lower motor neuron signs of the lower limbs (spastic displegia) and sensory segmental levels; one patient had lower limb paresthesia and lower limb weakness as main complaints. Two patients fulfilled SLE criteria exhibiting extra-neurological involvement: serositis, renal, haematological and cutaneous SLE respectively. Common identified serological markers were positive antinuclear antibodies and IgG anti-NMO antibodies and negative anti-dsDNA in all patients, and anti-Ro positivity in one patient. MRI revealed a similar pattern of extensive intramedullary demyelinating lesions (> 3 vertebral segments) involving the cervical spine in two, and the dorsal spine in all patients. Two patients were diagnosed with optic neuritis based on visual evoked potentials in the absence of symptoms; all patients fulfilled the revised diagnostic criteria for NMO2. Therapy with pulse methylprednisolone alone or in combination with cyclophosphamide (CYC, 0.5-7.5g/m^2 per month, 6 months) or plasma exchange lead to resolution or significant neurological improvement. Azathioprine or rituximab were administered as relapse prevention therapy, however one case developed optic neuritis in the course of disease and one case registered multiple myelitis relapses requiring repetitive rescue therapy with CYC.

Conclusions. In SLE patients with transverse myelitis, screening for optic neuritis (similarly to MS) in the absence of visual loss using visual evoked potentials may further aid diagnosis and improve outcome. Acute attack therapy with MP-CYC is effective; however sustained relapse prevention is mandatory as equivalent neurological manifestations in NMO/SLE relapse more frequent than neuropsychiatric SLE, leading to permanent neurological damage.

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Key words: transverse myelitis, Devic's syndrome, optic neuritis

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URINE LEUKOCYTES AS NON-INVASIVE MARKERS OF LUPUS NEPHRITIS

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Objective. Among the systemic lupus erythematosus (SLE) manifestations, lupus nephritis (LN) is one of the most severe symptoms, associated with a bad prognosis. Currently renal biopsy is the goal method for LN diagnosis. Since it is an invasive method, it is only carried out when the patient has clear symptoms of renal involvement. After the beginning of the therapy the clinical tools to monitor the responses of the patients are inefficient, and a second biopsy is not recommended, and the evolution of LN is followed up using indirect evidences. Thus, it is crucial to identify non-invasive biomarkers allowing and early diagnostic of LN.
Design and Method. To this aim, we have obtained urine samples (50 ml) from SLE patients with and without renal involvment, as well as from healthy donors following the ethical guidelines of the Servicio Andaluz de Salud. We have also set up several multicolor panels and a specific staining protocol, allowing the quantification of the major leukocyte populations in the urine including both mononuclear and polymorphonuclear cells. This protocol allows the quantification of the major leukocyte populations in the urine sediment, as a reflection of the renal immune infiltrates. In paralel, we have quantified the same populations in the blood by whole blood flow cytometry, using similar panels and standard procedures.
Results. From our data, the main cells associated with lupus neprhitis belong to the myeloid lineage, including mainly monocytes/macrophages and neutrophils. Hence, we have characterized in deep the phenotypes of these cells and their relationship with the renal involvement in lupus patients using specific markers, and compared the populations found in the urine with those present in the blood of the same donors and patients. We have also explored the relationship between the abundance of the different subsets in urine with histological and analitical parameters.
Conclusions. In this work we give evidences for an unexpected role of different subsets of myeloid cells (neutrophils and monocytes) in the pathogenesis of lupus nephritis, and their value as non-invasive biomarkers for renal involvement in systemic lupus erythematosus. Furthermore, the implications of these specific subpopulations in the pathogenesis of LN are discussed.

Key words: lupus nephritis, urine cytometry, non-invasive diagnosis

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POLYARTERITIS NODOSA VASCULAR LESIONS AS EARLY MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS - A CASE REPORT AND SYSTEMATIC LITERATURE REVIEW

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Objective. Small vessels vasculitis affects up to 11% of patients with systemic lupus erythematosus (SLE)1; medium and large vessel involvement is extremely rare and only occasionally reported.
Design and Method. Starting from our case, a complete literature review was conducted using searching engine in PubMed and as mesh terms, "polyarteritis nodosa", "vasculitis" and "systemic lupus erythematosus". We focused on clinical features, treatment strategy and outcomes.
Results. A 32-year old woman, with an episode of palpable purpura in the legs and arthritis in small joints of hands and feet in 2012, was admitted to our unit in December 2015 because of lower limb oedema with diffuse necrotizing ulcers, dry gangrene of both hand and foot fingers, livedo reticularis, small joint arthritis and low-grade fever lasting for two months. Blood test showed elevated erythrosedimentation rate, leucocytosis with neutrophilia, low serum complement, positive ANA (1:640 homogeneous pattern), low-level anti-dsDNA (52.7 KUI/L) and anti-Ro/SSA. Doppler of lower limbs revealed thrombosis in the right sural region and angiography showed total bilateral occlusion of tibial, interosseous and dorsalis pedis arteries. Skin biopsy showed severe necrotizing vasculitis involving both medium-sized and small vessels with an infiltrate mainly of mononuclear and polynuclear cells and few eosinophils. The patient was diagnosed with active SLE complicated by polyarteritis nodosa (PAN) vascular lesions. She was treated with

Table (P6: 141).

Author	Year	Patient	First symptom	Latecy	PAN organ involvement	Therapy	Outcome
Karani S	1953	45 y/F	SLE	4 y	Intestinal	Bismuth	Death
Paronetto F	1964	26 y/F	SLE	5 y	Liver	PDN	Death
Schneider H	1968	48 y/F	PAN	15 y	Skin	PDN	Successful
Martinez A	1987	42 y/M	DILE+PAN	0 y	Muscolar, PNS	PDN	Successful
Costa AG	1990	21 y/F	SLE+PAN	0 y	Cardiac	N/A	Death
D'Cruz D	1993	29 y/F	SLE	11 y	Skin, Renal	PDN/CYC	Successful
Vivancos J	1995	63 y/F	SLE	12 y	Systemic, PNS	PDN/CYC	Successful
Stratton R	1999	24 y/F	SLE	3 y	Intestinal, Renal	PDN/CYC	Successful
Ramos M	2006	63 y/F	SLE	12 y	PNS	N/A	N/A
		53 y/F	SLE	10 y	Skin, PNS	N/A	N/A
		44 y/F	PAN	3 y	Renal	N/A	N/A
		45 y/M	PAN	5 y	Skin, PNS	N/A	N/A
		61 y/F	SLE	15 y	PNS	N/A	N/A
Kumar N	2007	17 y/F	SLE+PAN	0 y	Skin, Gangrene, PNS, CNS	PDN/CYC	Successful
Marques LS	2015	9 y/F	PAN	5 y	Skin, PNS	PDN/CYC	Successful
Bhushan S	2016	30 y/F	SLE+PAN	0 y	Renal	PDN/MMF	Successful

SLE: systemic lupus erythematosus; PAN: polyarteritis nodosa; DILE: drug-induced lupus erythematosus; CNS: central nervous system; PNS: peripheral nervous system; PDN: prednisone; CYC: cyclophosphamide; MMF: mycophenolate; N/A: not available.

high-dose corticosteroids, intravenous prostanoid, plasmapheresis and, in addition, she underwent surgical debridement and right forefoot amputation followed by autologous split-thickness skin graft. A progressive improvement was observed.
Among 25 article found in literature, 12 were selected, which included overall 16 patients. Most of them were female (87.5%), mean age ± SD 43±16.9 years, with a long-lasting SLE (mean disease duration ± SD 7.5±4.6 years). In only four patients (26.6%) PAN and SLE co-occurred at the time of the diagnosis. The prominent PAN manifestation observed in association with SLE are reported in the Table. Notably, necrotizing ulcers and dry gangrene was present in only one case. The majority of the patients were treated with high dose prednisone and immunosuppressant; therapy was successful in eight out eleven patients (72.7%).
Conclusions. Vasculitis may be part of the pathological spectrum of SLE and, as in our case, it could be the prominent manifestation. The co-occurrence of PAN and SLE leads to a severe clinical condition with important prognostic and therapeutic implications.

Key words: polyarteritis nodosa, systemic lupus erythematosus, skin necrosis

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LUPUS NEPHRITIS IN QATAR

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Objective. To review histological types, clinical manifestations, laboratory findings and treatment outcome for Lupus Nephritis (LN) cases in Qatar.
Design and Method. We retrospectively analyzed the data of all patients with biopsy proven LN diagnosed between January 2006 and December 2014 at Hamad General Hospital, Doha-Qatar. Clinical, laboratory and treatment data were collected from the files and electronic records. Outcome at the end of 1st year of treatment was recorded.
Results. Our cohort included 50 patients; 43 (86%) were females and 7 (14%) were males with a ratio of 6:1.The median age at onset of LN was 29 years. The average interval between onset of Lupus and diagnosis of Lupus nephritis was 2.5 years.
The most common non-renal manifestations at the time of LN diagnosis were arthralgia (50%), arthritis (34%), fever (34%), and serositis (22%).
Class 4 was the most common type (44%), followed by class 3 (20%), class 5 (12%), class 2 (12%), Class 3+5 (6%), Class 2+5 (4%) and class 1 (2%) in our cohort.
Proteinuria alone was seen in 72% patients, renal insufficiency in 26% whereas nephrotic range proteinuria in 34% cases.
Anti ds-DNA was positive in 90% cases, Low C3 in 83% and low C4 in 59% cases at the time of LN diagnosis.
Mycophenolate mofetil (MMF) was the most commonly prescribed drug (74%), followed by Azathioprine (14%), and cyclophosphamide (6%). Pulse steroid was prescribed in 44% of cases, and oral steroid in 100% cases. Outcome at 1st year-end was available for 62% cases, of which 24% achieved complete remission (CR), 16% partial remission (PR) and 22% had treatment failure (TF). All of the CR cases and 75% of the PR cases were on Mycophenolate. CR was observed in 42.9% of class 4, 42.9% of class 3 and 20% of class 5 LN patients. Treatment responses in patients receiving MMF were as follows: CR in 50%, PR in 25% and TF in 25%.
Conclusions. The most common LN class in our cohort was Class 4, similar to those reported from most centers worldwide.
Further studies are required to look into the long-term outcome of our patients, especially the Qatari and Arab patients.

Key words: lupus nephritis, Qatar, outcome

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BELIMUMAB INDUCES REMISSION OF DERMATOLOGIC MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Systemic lupus erythematosus (SLE) is characterized by variable clinical course. SLE is characterized by various cutaneous manifestations, malar rash being one of them. Cutaneous manifestations in SLE are resistant to treatment, many drugs used having significant side effects. Nowadays, there are new drugs with a novel mechanism of action which are indicated for the treatment of patients with SLE, which may improve cutaneous manifestations. The aim was to describe the effect of belimumab on cutaneous manifestations in a cohort of SLE patients having had inadequate response to previous therapeutic regimens.
Design and Method. A cohort of five patients with SLE, 4 female and 1 male, aged 45, 49, 54, 68 and 36 years, respectively, is described. Belimumab was administered after inadequate response to treatment with corticosteroids, hydroxychloroquine, azathioprine, in one case mycophenolate mofetil, and in one case pulse cyclophosphamide. All patients had leucopenia, lymphopenia, positive anti-dsDNA antibodies, positive ANA and positive anti-Sm antibodies in two cases. Cutaneous manifestations, especially a malar rash was a prominent clinical feature in the patients described herein. In one case severe renal involvement was also present with membranoproliferative glomerulonephritis. In one case pulmonary involvement was present and in one case severe central nervous system involvement. All patients had fatique. In the patients studied 25(OH)D3 levels were measured.
Results. After belimumab treatment, fatique improved, cutaneous manifestations improved impressively, lymphopenia, leucopenia and thrombocytopenia normalized and complement levels improved. The characteristic malar rash almost disappeared completely in the patients described herein. Corticosteroid dosage was decreased in all cases. Low 25(OH)D3 levels were observed in 2 of the patients described.
Conclusions. Belimumab is a synthetic monoclonal antibody which inhibits B-cell activating factor (BAFF) indicated for the prevention and treatment of flares in SLE. Belimumab leads to clinical and laboratory improvement in SLE and a diminished need for corticosteroids. Belimumab has been reported to induce remission of cutaneous manifestations in subacute cutaneous lupus erythematosus. In the present study belimumab was shown to improve significantly the cutaneous manifestations in SLE patients. Belimumab, a long awaited drug for the treatment of SLE may prove useful for the management of cutaneous manifestations in SLE patients.

Key words: belimumab, cutaneous manifestations, malar rash

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ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA) IN LUPUS NEPHRITIS

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Objective. Anti-neutrophil cytoplasmic antibodies (ANCA) are considered a diagnostic marker for ANCA-associated vasculitis. However, they can be found in other diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. In particular, in lupus nephritis, their presence has been associated with pauci-immune necrotizing lesions resembling those of ANCA-associated vasculitis. The aim of our study was to analyze the prevalence of MPO and PR3 specific ANCAs in a population of 83 consecutives patients with active glomerulonephritis who underwent kidney biopsy, and to correlate ANCA positivity with clinical and histological data.
Design and Method. PR3 and MPO-ANCA were measured by ELISA (Euroimmun) in serum samples from 83 patients with biopsy proven lupus nephritis. These patients were part of a larger study including 107 patients with SLE, diagnosed according to the American College of Rheumatology criteria (94 females, 13 males) recruited in two Italian Renal Units (Fondazione Ospedale Maggiore

and Azienda Ospedaliera Ospedale San Carlo Borromeo, Milano), Serum samples were collected at the time of kidney biopsy and stored at -20°C until evaluated. The renal biopsies were classified following the ISN/RNP classification. Activity and chronicity indices were calculated according to Austin et al.
Results. ANCA were detected in 6 patients (7,2%); PR3-ANCA were found in 4 and MPO in 1; 1 patient was positive for both. All patients but one had a proliferative form of GN. None of them had a pauci-immune necrotizing GN.
Conclusions. PR3 and MPO-ANCA are found in a minority of patients with lupus nephritis. In our unselected series of cases, ANCA positivity was not associated with features of renal vasculitis. The small number of positive patients precluded further evaluation in order to find correlation with clinical and histological parameters.
In conclusion, PR3 and MPO-ANCA are rarely found in lupus nephritis and are not associated with histological signs of renal vasculitis.

Key words: ANCA, nephitis, biopsy

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ACUTE CARDIAC FAILURE AND IGA NEPHROPATHY: AN UNCOMMON SLE ONSET

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Objective. We report the case of a patient in who acute cardiac failure and IgA nephropathy were the first clinical manifestations of systemic lupus erythematosus (SLE). Cardiovascular support and immunosuppressive treatment allowed a long lasting remission.
Design and Method. A 45-year-old white man, with history of hypertension and smoking, was admitted to the hospital because of severe dyspnea and chest pain. He reported a three months history of progressive shortness of breath and fatigue. Clinical examination suggested an acute heart failure with elevated blood pressure (169/110 mmHg) and tachycardia (120 bpm). Laboratory findings showed increased troponin T (127.3 pg/mL), creatinine (2.5mg/dL), GOT (1355 UI/mL), GPT (1310 UI/mL), ferritin (4322 ng/mL) and CRP (2.58 mg/dL) levels. Urinalysis showed hemoglobinuria (3+) and proteinuria (0.3 g/L). Transthoracic Doppler echocardiography revealed a severe systolic dysfunction (LVEF: 15-20%) with normal valves and minimal pericardial effusion. Cardiac MRI detected two left ventricular areas of intramural myocardial delayed enhancement whereas coronary angiography was unremarkable. He was treated with intravenous inotropes, nitroglycerine and diuretics with improvement of the clinical status. Additional laboratory analyses showed anemia (Hb 10.8 g/dL), thrombocytopenia (73 x 103/μL), positivity of antinuclear (homogeneous pattern - 1:2560 titer), anti-double stranded DNA (164 IU/ml) and anti-Sm/RNP antibodies, and low complement levels (C3 0.449 g/l, C4 0.036 g/L). During hospitalization, the patient presented fever without any evidence of infection. A CT scan revealed pleural-pericardial effusion, splenomegaly and diffuse lymphadenopathy.
Results. According to clinical features and laboratory findings, a diagnosis of SLE was made and the patient was treated with methylprednisolone (1 g/day for 3 days) followed by oral prednisone (1 mg/kg/day) with remission of fever and improvement of hematological values. However, urinalysis confirmed hemoglobinuria (3+) and proteinuria (0.63 g/24h). These findings lead us to perform renal biopsy. Histology revealed moderate mesangial sclerosis with segmental proliferation and indirect immunofluorescence detected IgA (+++), C3 (+++) and IgG deposits (+). According to current criteria, histology was defined as IgA nephropathy (HAAS classification, class III). Prednisolone dose was tapered up to 25 mg/day in 4 months and hydroxychloroquine (200 mg twice a day) was added. After 6 months' follow up we switched hydroxychloroquine to mycophenolate mofetil (1000 mg twice a day). Transthoracic Doppler echocardiography revealed improvement of left ventricular function (until 55% of ejection fraction) and urinalysis showed regression of proteinuria and hemoglobinuria. Nowadays, the patient is in good clinical conditions with a maintenance dose of prednisone (2.5 mg/day) and mycophenolate mofetil.
Conclusions. This case reports and uncommon SLE onset with the association of acute cardiac failure and atypical renal involvement.

Key words: heart, kidney, IgA

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CARDIAC INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Objective. Cardiac involvement is common in systemic diseases and sometimes it is an important element of diagnostic or prognostic. In systemic lupus erythematous (SLE), cardiac events can range from multiple valve damage to a marked increase in cardiovascular risk, but the pericardium and endocardium are most often affected.
These events are the result of several factors such as inflammation, cardiovascular risk factors or concomitant treatments (corticosteroids in particular). Cardiovascular diseases are the cause of mortality and considerable morbidity in these patients. The aim of this study is to analyze the cardiac events in patients with the diagnosis of SLE in order to assess whether the cardiac event are clinically significant and whether they involve management, monitoring or special treatment.
Design and Method. We analyze cardiac events in patients with the diagnosis of SLE admitted to a cardiology department of a central hospital, over a period of two years. We take into account the clinical manifestations, laboratory parameters related to flair and cardiac involvement evaluated by echocardiography data and coronarography.
SLE disease activity was assessed using the SLE Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group disease activity index (BILAG). We investigate by echography valve damage, systolic and diastolic dysfunction, the effects of disease activity on left ventricular (LV) regional functions and the presence of pericardial effusion in SLE patients.
We analyze the relationship between cardiac symptoms and findings of coronary angiography.
Results. Twenty SLE patients (18F/2M) with mean age of 54.8 (21/94 years) with cardiovascular symptoms were evaluated by echocardiography.
We report 14/20 patients with valve events; valvular alterations were kind fibrosis and thickening of the mitral valve and aortic, affecting significant valvular regurgitation. The moderate pulmonary hypertension (5/20), diastolic dysfunction of the left ventricle (13/20) and pericardial effusion were frequent findings (6/20 with pericarditis and pericardial effusion, none with cardiac tamponade).
The presence of cardiac alterations, including the valvular fibrosis process was independent of age.
Among the symptomatic patients, 9 had an abnormal angiogram with one or more plaques, while 4 had normal angiograms. All seven asymptomatic patients had normal angiograms.
Conclusions. The cardiac alterations associated with SLE are frequent, to highlight the elevated prevalence of left valvular fibrosis which was not associated with age or the presence of other forms of cardiac involvement such as pulmonary hypertension and diastolic left ventricular dysfunction. The cardiac investigation – echocardiography and coronarography – is helpful in predicting cardiovascular prognosis, in management, monitoring and special treatment.

Key words: cardiac involvement, monitoring of cardiac lupus, coronarography

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SHRINKING LUNG SYNDROME AS A PULMONARY COMPLICATION OF JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE REPORT

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Objective. To describe a case of shrinking lung syndrome (SLS) in a teenage female patient with juvenile systemic lupus erythematosus (jSLE).
Design and Method. Description of a case according to the data of medical records.
Results. Undifferentiated connective tissue disease was diagnosed at the age of 10 years (May 2008) and treatment with hydroxychloroquine (HCQ) was started. During next 7 years the disease remained clinically controlled with treatment. In March 2015 during a flare, the criteria of jSLE (arthritis, haematological changes, antinuclear antibody positivity and presence of anti-Sm nuclear antigen) were fulfilled; corticosteroid (CS) and azathioprine (AZA) were added to treatment. After stopping of CS an exacerbation followed and a small dose CS was

started again. In June 2015 the patient started complaining episodic chest pain and dyspnea. Laboratory tests were practically in normal limits. Pulmonary function tests (PFTs) showed marked restrictive changes (forced vital capacity (FVC) 53.4%, total lung capacity (TLC) 68.2%). On chest x-ray reduced lung volumes and elevated hemidiaphragms were seen; computed tomography of lungs showed elevated right hemidiaphragm, minimal right pleural effusion and no parenchymal changes. Ultrasonography (US) showed decreased diaphragmal movement (right side 3-5 mm and left side 1-6 mm). SLS was diagnosed. Intravenous CS pulse-therapy was started (10 mg/kg/dose) and the dose of oral prednisolone was increased to 1 mg/kg/day. After the first pulse-therapy dyspnea and chest pain resolved within days, in US normalised diaphragmal movement was described after one week, spirography showed also positive dynamics, but did not normalise. At the end of September the patient discontinued CS without consulting her physician; the treatment with HCQ and AZA was continued. During December 2015 episodic chest pain and dyspnea reoccurred, imaging studies and PFTs showed the same changes as in June 2015 and laboratory tests supported a flare of SLS and jSLE. After restarting CS the symptoms resolved within a week again; radiological investigations and PFTs showed improvement. Treatment with AZA was changed to mycophenolate mofetile.
Conclusions. SLS is a rare pulmonary complication of jSLE. According to literature symptomatic improvement occurs in few weeks after starting the treatment but normalization PFTs may take longer like it was with our patient.

Key words: shrinking lung syndrome, juvenile SLE, complication

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EVALUATION OF CURRENT AND AT THE ONSET CLINICAL MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Objective. To analyze the influence of age and years of disease on the current clinical manifestations and the debut of the disease in patients with SLE.
Design and Method. Cross-sectional prospective study of SLE patients according to the SLICC-2012 criteria, coming from the Rheumatology Service of La Fe Hospital and Arnau de Vilanova Hospital. All patients had a complete blood-test with autoimmunity markers, and clinical, biometrics and treatment data were also collected from the personal interview and the medical history. Biostatistical analysis of the data was performed using the R software version 3.2.3.
Results. A total of 142 patients were evaluated; (94% women) with mean age of 47.40±12.84 and 9.99±10.57 year-evolution of SLE. We can find the clinical manifestations at the onset disease in the table.

Onset Manifestation	(%)
Musculoskeletal	73.6
Skin	39.3
Kidney	5
Cytopenia	7.9
Sjögren Syndrome	2.9
Raynaud's	15
Others	27.1

We observe statistically significant differences in the musculoskeletal system involvement (p=0.008), and in the presence of vasculitis (p=0.01) in patients with a shorter time of disease evolution. There is also a direct relationship between cardiovascular (p=0.002) and renal (p=0.03) affection in younger patients. Finally, cytopenias are correlated both in young patients (p=0.0009) as well as with a shorter time of evolution (p=0.02).
Conclusions. We observe a concordance between our SLE series and those already described at the literature, where renal involvement occurs at younger ages, and the musculoskeletal system involvement occurs early in disease or even as the onset symptom.

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Key words: clinical manifestations, onset manifestation

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SYSTEMIC LUPUS ERYTHEMATOSUS AND AUTO IMMUNE HEPATITIS: A CASE REPORT

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Objective. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder involving various organs such as kidneys, skin and the central nervous system. Liver involvement is normally not part of the spectrum of SLE, but is seen in up to 60% of SLE patients. Hepatotoxic drugs, coincident viral hepatitis and non-alcoholic fatty liver disease (often induced by steroids) are the most commonly described causes of elevated liver enzymes in SLE.
Liver diseases that accompany Systemic Lupus Erythematosus (SLE) disease activity generally have good prognosis and do not progress to cirrhosis.
Design and Method. The clinical presentation of AIH ranges from asymptomatic disease recognized only by incidentally biochemical abnormalities to an acute or even fulminant hepatitis. Female predominance and occurrence peaks in early adult life and in the 4th decade of life are characteristic. In symptomatic cases patients are often affected by non-specific symptoms such as nausea, anorexia, abdominal discomfort and jaundice. A common extrahepatic manifestation of AIH may be arthralgia, which is also often seen in SLE.
While elevated IgG and anti-nuclear antibodies (ANAs) are characteristic for both AIH and SLE, there are few serological markers, which are highly specific for the two different diseases. Anti-double stranded DNA (anti-dsDNA) antibodies are associated with SLE but are also found in patients suffering from AIH. Specific markers for AIH, which usually do not occur in SLE, are soluble liver antigen (SLA), Liver-pancreas, smooth-muscle antibody (SMA) with specificity for F-actin and microsomal autoantigens, such as anti-liver kidney antibodies (anti-LKM antibody).
Results. The author´s present a case report of a female patient with 30 years old, diagnosed for LES in 2005 in immunosuppressive therapy for almost 10 years with Methotrexate and Cyclosporine, with recent aggravating complaints for knee and elbow arthralgia with morning rigidity over 2 hours, abdominal pain with episodic fever and fatigue. In recent laboratory tests evaluation, beside the homogeneous ANA pattern with rising titers and specific antibodies for LES, we found a citoplasmatic filamentous pattern suggestive for ASMA, found to be F-actine antibodies confirmed in VSM 47 transfected cells, with borderline liver function tests.
Conclusions. The co-occurrence of LES and AIH is rare, and few cases are reported in the literature so far.

Key words: systemic lupus erythematosus, auto immune hepatitis, F actine antibodies

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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)-ADOLESCENT PSYCHOSIS. A CASE DESCRIPTION

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Objective. There is evidence of neuropsychiatric factors that contribute to the development of autoimmune diseases. The incidence of neuropsychiatric disorders in patients with SLE is 80-91% and are the causing agents of high morbidity and mortality rates. There are five groups of psychiatric disorders (mood disorders, anxiety disorder, cognitive dysfunction, psychosis and acute confusional state). Usually, the psychiatric evaluation of these patients reveals psychopathological disorders while they report a period of intense psychological stress in their background.
Design and Method. To describe a case of a patient with SLE and neuropsychiatric manifestations- a condition that is likely not to be recognized and subsequently this can lead to a late diagnosis of the disease.
Results. A 13-year-old female adolescent was hospitalized so as to evaluate an episode of fever, headache and arthralgias. Fever, coughing, a rash on the palms and cheeks were reported in the background during a period of 20 days while loss of weight during the last month and amenorrhea during the last three months were also reported. The adolescent whose parents were separated, developed psychosis-like behavioral disorders .The laboratory evaluation revealed: the cerebrospinal fluid analysis was normal. She was also negative to antibodies against Rickettsia, Borrelia, Leishmania, Mycoplasma, EBV while the wright test for Brucella and the Mantoux test were negative. These results excluded the possibility of an infection. The imaging tests excluded the possibility of a mass lesion. The rest of the laboratory evaluation revealed: WBC:2770 mm^3. PLT:60000/mm^3, Hb:9.01 g/dl, ESR:80mm/h ,high levels of protein in a 24h urine collection, low levels of IgG and IgE antibodies, low C3 and C4 complement levels, high levels of ANA (INOVA Daignostics, USA) and cardiolipin antibodies. The diagnosis was conducive to SLE with intense central nervous system involvement.
Conclusions. The central nervous system involvement is one of the least conceivable manifestations of SLE. Even though neuropsychiatric manifestations precede, they rarely lead to a diagnosis of the disease. An on-time diagnosis is important and clinical judgment should point to this direction as early as possible.

Key words: neuropsychiatric manifestation, central nervous system, adolescent

Poster session 7: Cardiovascular disease and antiphospholipid antibodies

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EVALUATION OF THROMBOTIC RISK IN PATIENTS WITH POSITIVE ANTIPHOSPHOLIPID ANTIBODIES WITHOUT CLINICAL CRITERIA FOR THE DISEASE

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Objective. Antiphospholipid antibodies (aPL) have a strong relationship with thrombosis and pregnancy morbidity. However, the value of each type of aPL as a marker to develop antiphospholipid síndrome (APS) is not fully clarified.
Objectives
a)To analyze the incidence of thrombosis in patients with positive aPL who do not meet clinical criteria for APS. b)To identify possible risk factors for thrombosis. c)To analyze the possible protective role of primary thromboprophylaxis.
Design and Method. Retrospective study of patients with positive aPL (medium or high titers) at least 2 times, separated by a minimum of 12 weeks, without fulfilling clinical criteria for APS. The presence of vascular events was confirmed with imaging test.
Results. After a mean follow up of 146±60.3 months, 13 (9.4%) patients developed thrombosis. The mean time to thethrombotic episode was 81.4±41.7 months. Several classic cardiovascular risk factors (CVRF) such as tobacco use, hypertension and dyslipidemia(DLP) were more frequent in patients with thrombosis being also independent risk factors for thrombosis in the univariate analysis, with an OR of 6.5 for hypertension, 5.3 for tobacco use and 10.5 for DLP. Regarding the different antibodies, only the lupus anticoagulant (LA) (p=0.062) and anticardiolipin antibodies (aCL) IgM (p=0.14) tended to be more frequent in patients with thrombosis. Positiviy for the 3 types of antibodies was associated with increased risk of thrombosis (OR 7 [95%IC 1.9-28.5]; p=0.004). Multivariate analysis showed the following independent risk factors for thrombosis: smoking (OR 8.3 [95%CI 1.3-52.5]; p=0.024), hypertension (OR15.9[95%CI 1.8-138.7]; p=0.012), DLP (OR16.9[95%CI 1.4-108.3]; p=0.027) and IgM aCL (OR18.7[95% CI 12-277.7]; p=0.033). Among 13 thrombotic events, 10 were arterial and 3 venous. Regarding treatment, 102 patients received prophylaxis with ASA 100 mg/day, showing a tendency towards protection (OR 0.774 [95%CI 0.2-2.7] p=0.686).
Conclusions. The incidence of thrombosis in patients with positive aPL that do not meet clinical criteria for the disease is about 10%. Tobacco use, DLP, hypertension and IgM aCL are independent risk factors. Higher load of antibodies increases the risk for thrombosis. The protective role of aspirin seems to be limited in this population, thus thromboprophylaxis with anticoagulation in high risk patients should be considered.

Key words: antiphospholipid antibodies, thrombosis, risk factors

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RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS EXHIBIT SIMILAR DEGREE OF SEVERITY OF SUBCLINICAL ATHEROSCLEROSIS. RESULTS FROM A CROSS-SECTIONAL STUDY IN A POPULATION OF NORTHWESTERN SPAIN

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Introduction. Chronic inflammation plays a central role in the development of atherosclerosis, being especially relevant in patients with rheumatic diseases. Patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are more prone to suffer cardiovascular events than the general population.

Objectives. Our aim was to study the prevalence of subclinical atherosclerosis in patients with RA and SLE and determine the differences between these conditions.
Design and Method. We evaluated 99 SLE patients and 206 sex- and age-matched RA patients without previous history of cardiovascular events. Subclinical atherosclerosis was defined by the presence of carotid plaque according to Manheim Consensus Conference criteria and/or intima-media thickness > or equal to 0.90 mm. Carotid ultrasonography was performed by a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7–12 MHz linear transducer and the automated software guided technique radiofrequency – Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland). After the univariate analysis, multivariate regression models were fitted to adjust for potential confounders.
Results. The mean age was 52±13 years in RA and 51±13years in SLE (p=0.77). Demographic data and traditional cardiovascular risk factors are summarized in Regarding carotid plaques, there were no statistically significant differences. The frequency of carotid plaques was 40.2% among patients with RA and 44.4% in SLE patients. Bilateral plaques were present in 26% patients with RA and in 21.2% of those with SLE.
An IMT > or equal to 0.90 mm was observed in 9.8% RA patients and in 6.3% of SLE patients (p=NS) .
After adjusting for traditional cardiovascular risk factors and disease duration, there were no differences in the frequency of carotid plaques (OR SLE vs RA 1.52; CI 0.88-2.62) or in the frequency of IMT > or equal to 0.90 mm (OR 0.75; CI 0.27-2.07).

Table I.

	SLE, % (n=99)	RA, % (n=206)	*p*
Female	93.9	95.1	0.784
Age (mean ± SD) years	51.4±13.4	51.9±13.5	0.768
Disease duration (Mean ± SD) years	11.1±8,5	8.6±8.3	0015
Hypertension	25.3	31.9	0.284
Dyslipidemia	19.2	42.2	<0.001
Diabetes	1.0	8.3	0.009
Smokers former smokers	24.2	33.8	0.084
Family history of premature CV disease	29.6	19.2	0.055
Carotid plaque	44.4	40.2	0.535
Plaque unilateral	23.2	13.7	
bilateral	21.2	26.5	0.104
IMT ≥ 0.90 mm	6,3	9.8	0.383

Conclusions. The frequency of subclinical atherosclerosis is similar in patients with SLE and RA after adjusting for traditional cardiovascular risk factors.

Key words: rheumatoid arthritis, systemic lupus erythematosus, subclinical atherosclerosis

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CORONARY ARTERY CALCIFICATION IN DANISH SLE PATIENTS WITHOUT KNOWN CARDIOVASCULAR DISEASE: COMPARISON WITH MYOSITIS, DIABETES AND THE GENERAL POPULATION

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Objective. Patients with systemic lupus erythematosus (SLE) have a high risk of cardiovascular disease (CVD) which is thought to be due to accelerated atherosclerosis. Coronary artery calcification (CAC) is a marker of coronary atherosclerosis and is found to be highly prevalent in patients with SLE.
The aim of this study was to determine the prevalence and extent of CAC as well as traditional cardiovascular (CV) risk factors in SLE patients without prior CVD compared to a subset of the general population and to patients with another connective tissue disease, idiopathic inflammatory myopathies (IIM) and to patients with diabetes mellitus (DM) without prior CVD.
Design and Method. In this cross-sectional study 104 SLE patients, 2,237 controls from the general population, 69 IIM patients and 175 DM patients were screened for CAC and CV risk factors. In all cohorts patients with CVD were excluded. CAC was measured in Agatston score and classified as high CAC (>399 U) and extreme high CAC (>1000 U). To compare the groups with respect to the prevalence and extent of CAC and CV risk factors multivariate logistic regression was used.
Results. The SLE patients were younger and more females as compared to the general population, to IIM and DM patients. After controlling for CV risk factors including age and gender SLE patients showed to have a substantially high odds ratio (OR) for high and extreme high CAC compared to: the general population (OR 6.9, 95% CI 3.2-14.9 and 10.1, 95% CI 3.5-28.6), IIM patients (OR 2.6, 95% CI 0.8-8.6 and 10.1, 95% CI 1.2-82.2) and DM patients (OR 3.9, 95% CI 1.4-10.6 and 5.0, 95% CI 1.4-18.2).
Conclusions. In the setting of individuals without CVD SLE patients independently of traditional CV risk factors have more severe coronary atherosclerosis not only compared to the general population, but also compared to patients with IIM and DM.

Key words: cohort study, coronary artery calcification, cardiovacular risk factors

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PREVALENCE OF COMORBIDITIES IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS: A COMPARATIVE, REGISTER-BASED STUDY WITH EMPHASIS IN CARDIOVASCULAR DISEASE

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Objective. Reliable data regarding the prevalence of specific medical comorbidities among patients with Primary Sjögren's Syndrome (pSS) remain sparse and there are not comparative studies between patients with pSS and patients with Systemic Lupus Erythematosus (SLE). To compare the prevalence of the main comorbidities of two large cohorts of patients with pSS and SLE, with focus in cardiovascular (CV) diseases.
Design and Method. Transversal multicenter study where cumulative prevalence of relevant comorbidities, with identical definition in both cohorts, was compared. Patients in follow-up from SJOGRENSER (Spanish register of pSS) and RELESSER (Spanish register of SLE), meting AECG-2002 and ACR-97 classification criteria, were included. A binomial logistic regression analysis was carried out to explore potential differences, making general adjustments for age, sex and disease duration and specific adjustments for each variable, including CV risk factors and treatments.
Results. 437 SSp patients (95.2% female) and 2960 SLE patients (89.5% female) were included in the analysis. Mean age: 58.6 (p55-p75: 50.0-69.9) and 46.4 years (22.4-41.6) respectively (p<0.001). Disease duration 10,4 (6.0-16.7) and 13.3 years (8.80-20.04), respectively (p<0.001). The differences in the prevalence of the comorbidities are shown in theTable I. Smoking and Hypertension were more frequent in SLE as also they were the life-threatening CV events, *i.e.* ictus or myocardial infarction. The same thing happened with severe infections, also more frequent seen in SLE, but this difference lost statistical significance when adjusted for glucocorticoid (GC) and immunosupressors (IS) use. Patients with pSS were hospitalized by the disease activity lesser than SLE: 17% vs 53%, p<0.001; OR 0.18 (95%CI:0.14-0.24). Moreover, the use of GC or IS were less prevalent in pSS [GC: 49.4% in pSS vs 88.2% in SLE; OR:0.13 (95%CI:0.10-0.16); azathioprine: 10.1% vs 32.4% (OR: 0.24;IC95%: 0.17-0.33); mycophenolate: 3.9% vs 16.2% (OR:0.21;95%CI: 0.13-0.35); cyclophosphamide: 3.0% vs 22.6% (OR: 0.11;95%CI: 0.06-0.18)].
Conclusions. pSS patients have less serious comorbidity burden comparing with SLE, namely less CV diseases and less infections. In contrast, the risk of lymphoma exceeds that seen in SLE patients. The higher prevalence of CV events in SLE not seem to be explained just be classical CV risk factor, suggesting that SLE derived factors could be involved.

Key words: Lupus, Sjögren's syndrome, cardiovascular

Table I (P7:157). Comparative prevalence of comorbidities (pSS versus SLE without sSS).

Comorbidities	pSS N (%)	SLE N (%)	p value	OR (95%CI)	OR adjusted*	specific adjust#
Hypertension	112 (25.3)	804 (27.3)	0.454	0.92 (0.72-1.15)	0.44 (0.33-0.58)	-
Diabetes	28 (6.4)	122 (4.2)	0.005	1.84 (1.20-2.83)	0.84 (0.51-1.37)	-
Dyslipidemia	145 (33.2)	847 (29.7)	0.435	1.12 (0.90-1.8)	0.79 (0.63-1.01)	-
Smoking (any time)	110 (25.3)	1430 (48.2)	<0.001	0.25 (0.20-0.33)	0.50 (0.40-0.64)	-
Heart failure	13 (2.9)	87 (2.97)	0.991	1.00 (0.55-1.81)	0.35 (0.18-0.66)	ND
Ischaemic cardiopathy	4 (0.92)	83 (2.8)	0.019	0.25 (0.09-0.67)	0.22 (0.07-0.67)	GC, smoking HBP
Peripheral artery disease	14 (3.2)	58 (1.99)	0.103	1.63 (0.90-2.95)	0.84 (0.38-1.82)	GC, smoking HBP
Stroke	15 (3.4)	145 (4.9)	0.165	0.68 (0.40-1.17)	0.48 (0.25-0.94)	GC, smoking HBP
Cardiovascular events	30 (6.8)	253 (8.5)	0.24	0.79 (0.53-1.17)	0.53 (0.32-0.87)	GC, smoking HBP
Fibromyalgia	64 (14.6)	150 (5.2)	<0.001	3.13 (2.29-4.28)	2.70 (1.93-3.80)	ND
Osteoporotic fracture	37 (8.6)	153 (5.3)	<0.001	1.67 (1.14-2.42)	0.94 (0.60-1.45)	GC
Cancer(except lymphoma)	21 (4.8)	124 (4.2)	0.539	1.16 (0.72-1.86)	0.68 (0.41-1.15)	ND
Lymphoma	7 (1.6)	10 (0.3)	0.002	4.81 (1.82-12.71)	5.71 (1.83-17.79)	IS, HCQ
Serious infection	44 (10.1)	497 (17.7)	<0.001	0.52 (0.37-0.72)	0.75 (0.51-1.12)	GC, IS, HCQ

*OR pSS versus SLE, adjusted just by sex, age and disease duration, if not otherwise stated in the right column.
#Further specific adjust for each variable when applicable. ND: not done: pSS: primary Sjogren's syndrome; sSS: secondary SS; SLE: Systemic Lupus Erythematosus; CV: cardiovascular; HBP: high blood pressure; HCQ: hydroxychloroquine; GC: glucocorticoids; IS: immunosuppressor.

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DISEASE CHARACTERISTICS, SURVIVAL ANALYSIS AND MORTALITY IN A SINGLE CENTRE COHORT OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Objective. Significant mortality and morbidity has been reported in patients with antiphospholipid syndrome (APS). The main objective of this study is to characterize a single center cohort of patients with APS (including non-criteria manifestations) and to assess their survival rate, mortality reasons and associations with disease characteristics.
Design and Method. 240 patients with APS were studied. Demographic characteristics, cumulative clinical and laboratory features, autoantibody profiles were retrieved from the existing database. Unattending patients were contacted by telephone and were searched on the national death information system (NDIS). Patients who were non-responsive to telephone calls, not seen in the outpatient clinic within the last 6 months and could not be traced on the NDIS were considered lost-to follow-up.
Results: 118 had primary APS and 122 had APS associated with SLE. 83% were female. Mean age at diagnosis was 41±12, duration of disease and follow-up were 110±85 and 92±82 months.
65% of patients had vascular thrombosis (VT), 24% had pregnancy morbidity (PM), 10% had both VT and PM and 3 had catastrophic antiphospholipid syndrome. Overall 29% patients had thrombotic risk factors among which smoking followed by homozygous factor V Leiden mutation were the most prevalent. Of patients with VT 49% had arterial (A), 38% had venous (V) and 13% had both. 95 patients experienced a single thrombotic episode whilst 62 had more than once, most commonly V followed by A. In the PM group, there were 31 patients with fetal deaths beyond 10 weeks, 39 with 3 or more abortions before 10 weeks, 18 with premature labour and 14 with pre-eclampsia. Overall, 46% of patients had aCL IgG, 36% had IgM and LA was present in 54%. Anti beta2GPI was tested in 117 patients and 38% were positive for IgG and 25% for IgM. Of the non-criteria manifestations of APS, the most common presentation was heart valve lesions followed by thrombocytopenia.
In total there were 25 deaths and 19 patients were lost to follow-up. Survival rates were 94, 86, 78 and 71% at 5, 10, 15 and 20 years. Survival of patients with VT was markedly reduced (p=0.04).
Causes of death could be identified in 19 patients: 3 alveolar hemorrhage, 7 myocardial infarction, 1 intestinal perforation and sepsis, 2 liver infarct-abcess-sepsis, 1 malignancy, 3 Budd-Chiari, 2 pulmonary hypertension. Mortality was significantly associated with LA positivity (p=0.02). Among clinical manifestations patients with alveolar hemorrhage (p=0.002) and Budd Chiari syndrome (p=0.01) displayed a significantly higher mortality rate.
Conclusions. In this cohort, the most prevalent manifestation of APS was A thrombosis. Long-term follow up revealed that patients with APS had significant mortality and APS-related manifestations dominated the causes. Thrombotic patients had a reduced survival relative to PM patients. LA positivity was a risk factor for reduced survival.

Key words: antiphospholipid syndrome, survival, cohort

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THE RISK OF CARDIOVASCULAR MORTALITY AND DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS – A DANISH NATIONWIDE POPULATION-BASED COHORT STUDY

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Objective. To examine the risk of cardiovascular mortality (CVM) and cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, in patients with systemic lupus erythematosus (SLE) with and without lupus nephritis (LN) compared with a population-based control group.
Design and Method. In the Danish National Patient Registry we identified all incident SLE cases from 1995 to 2011. For each case, five sex- and age-matched population controls were selected. Incident events of MI, stroke and CVM were accounted for. Hazard ratios (HR) were calculated using Cox proportional hazard models; full adjustment included age, sex, Charlson's comorbidity index, cardioprotective medication, socioeconomic index, previous events of stroke and MI.

	MI	Stroke	CVM
SLE, all	2.50 (1.63-3.83)	2.15 (1.59-2.90)	1.65 (1.12-2.43)
SLE <40 years	4.28 (1.15-16.03)	5.16 (2.27-11.77)	9.98 (1.00-99.97)
SLE 40-55 years	3.07 (1.53-6.16)	3.12 (1.86-5.23)	1.20 (0.43-3.35)
SLE >55 years	1.97 (1.13-3.44)	1.45 (0.96-2.17)	1.65 (1.09-2.50)
SLE without LN	2.04 (1.28-3.24)	2.00 (1.45-2.76)	1.39 (0.91-2.11)
SLE with LN	10.79 (3.20-36.46)	3.56 (1.61-7.88)	5.35 (1.91-14.96)

Results. The study included 1644 SLE patients (86% women) and 8220 controls; 233 of the SLE patients (76% women) developed LN during follow-up. Mean age at cohort entry of SLE patients and controls was 47.2 years, though 42.5 years for the patients with LN. The number of events of MI, stroke and

CVM in the SLE group was 48, 92 and 56, respectively; the risk of these events was increased for SLE patients in general with HR's of 2.50, 2.15 and 1.65, respectively. These risks were higher among subjects <40 years of age and in patients with LN. For the latter the corresponding HR's were 10.79, 3.56 and 5.35, respectively.
Conclusions. Patients with SLE had increased risk of CVD and CVM compared with controls; especially in the subsets of patients with LN and younger age. In particular, the risk of MI was increased among patients with LN.

Key words: lupus nephritis, cardiovascular disease, cardiovascular mortality

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ARTERIAL WALL STIFFNESS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Arterial stiffness is enhanced in atherosclerosis and it is also associated with an increased risk for cardiovascular events. It has also been suggested as a surrogate measure of subclinical atherosclerosis in SLE. We examined the arterial stiffness of the right carotid artery by an ultrasound method in SLE patients and in population controls. Our aim was to investigate if arterial stiffness is increased in SLE patients and to test the possibility of using this method for vascular risk stratification in patients with SLE.
Design and Method. 305 patients with SLE and 290 population controls matched for age, sex and region of living were included during 2004-2013. All patients fulfilled at least four of the 1982 revised classification criteria for SLE according to the American College of Rheumatology (ACR). Cardiovascular disease (CVD) events were defined as objectively verified coronary heart disease, cerebrovascular disease or ischemic peripheral vascular disease. All subjects were investigated with ultrasound to monitor diameter (D) changes of the right common carotid artery, and blood pressure (P) was measured to calculate an arterial stiffness index, Stiffness index = ln(Psystolic/Pdiastolic)(D systolic-D diastolic)/D diastolic.
Results. Mean age was 48±14 years in SLE patients and 49±15 years in controls (ns). Manifest CVD was more common in patients (10% vs 1 %) (p<0.001). Systolic blood pressure was 118±17 mmHg in SLE patients and 119±16 mmHg in controls (ns). Hypertension, defined as a systolic BP>140 mmHg and/or a diastolic BP>90 mmHg or use of antihypertensive drugs was more common among patients (43 % vs 23 %, p=0.001).
Stiffness index was 5.7±2.4 in SLE patients and 4.8±2.1 in controls (p<0.0001), that is, SLE patients had stiffer arteries than controls. The result remained when excluding the patients and controls with a history of CVD. There was no difference in stiffness values between patients with or without a history of nephritis. In all subjects the stiffness index is correlated to age (r=0.50) systolic blood pressure (r=0.34), cystatin C (r=-0.28), presence of plaque (r=0.23), any arterial event (r=0.18), P-glucose (r=0.17), triglycerides (r=0.15), BMI (r=0.20) and waist circumference (0.21), cholesterol (r=0.15), a history of nephritis (r=0.11), LDL (r=0.11), ApoA/apoB r=0.11), ever smoking (r=0.09). In a multiple regression analysis
Conclusions. Manifest CVD was more common among SLE patients. Arterial stiffness measured in the right common carotid artery was increased in SLE patients compared with population controls and the difference remained when excluding all subjects with known CVD. Stiffness increased with age in SLE patients and controls.

Key words: arterial wall stiffness, cardiovascular disease, ultrasound

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SERUM GALECTIN-3 BINDING PROTEIN IS A NOVEL INDEPENDENT PREDICTOR OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. SLE patients have a marked increased risk of venous (VTE) and arterial (AT) thrombosis, which is not fully explained by traditional risk factors or the presence of anti-phospholipid antibodies. A better understanding of this and new biomarkers to identify risk patients are needed. Increased type I interferons (IFNs) frequently found in SLE patients, and macrophage activation may promote atherosclerosis and thrombogenesis. Interferon-γ-inducible protein 10 (IP-10) and galectin-3 binding protein (G3BP) are induced by type I IFNs, and sCD163 reflects macrophage activation. Moreover, G3BP is elevated in serum/plasma and on circulating microparticles in SLE. G3BP upregulates P-selectin on platelets and facilitates cellular and platelet adhesion to the thrombus and endothelium promoting thrombogenesis. We explore serum G3BP, IP-10, and sCD163 levels as predictors of venous and arterial thrombotic events in a long-term follow-up period in a large cohort of Scandinavian SLE patients.
Design and Method. Baseline clinical and serological data and serum were available from 175 SLE cases. VTE and AT follow-up data were available with a median follow-up period of 6 years. Baseline serum G3BP, IP-10, and sCD163 were quantified using ELISA. Univariate comparisons, binary logistic regressions, and Cox regression analyses were conducted to evaluate the association between VTE/AT and serum G3BP, IP-10, sCD163, and baseline data.
Results. A total of 13 VTE events (7.4%) and 14 AT events (8%) were recorded in the follow-up period. Baseline serum G3BP, IP10, and sCD163 did not differ significantly between event and non-event subjects for neither VTE nor AT. However, G3BP serum levels associated positively with the risk of VTE in a Cox regression model stratified on age (hazard ratio (HR)=1.09, p-value = 0.04) and persisted when adjusting for gender, traditional risk factors, antiphospholipid syndrome (APS), previous VTE, disease duration, disease activity, and medication (HR=1.13, p-value = 0.03). Apart from age and APS, none of the other covariates correlated with increased risk of thrombosis.
Conclusions. Our findings support circulating G3BP as a novel independent predictor of VTE in SLE that may aid in future VTE risk stratification and prophylaxis. Furthermore, the results provide indications of a pathogenic link between G3BP, type I IFNs, and VTE in SLE.

Key words: G3BP, VTE, biomarkers

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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN): A NEW MANIFESTATION OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS)?

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Objective. Intraductal papillary and mucinous neoplasia (IPMN) is a rare pancreatic exocrine tumor. Endoscopic ultrasonography (US) and magnetic resonance cholangiopancreatography are used for diagnosis. Due to the high rate of invasive malignancy in patients with IPMN involving the main duct and the good prognosis after pancreatic surgery, surgical resection is recommended. Branch-duct IPMN with absent or limited symptoms and no findings suggestive of malignancy can be observed without resection.
Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening disease characterized by multiple small-vessel occlusions of rapid onset.
We describe 3 patients with CAPS who further presented IPMN-like lesions on

concordant imaging studies, which led to unnecessary pancreatectomy in the first case.
Design and Method. The diagnosis of CAPS was based according to international classification criteria [Asherson RA, et al.: *Lupus* 2003; 12: 530-4].
Results. All patients had a history of CAPS months or years before the IPMN diagnosis. They had abdominal pain or abnormal liver test results and had undergone radiography.
In a 36-year-old man, endoscopic ultrasonography and magnetic resonance cholangiopancreatography demonstrated parietal thickening, stenoses and dilatations of the main pancreatic duct, which suggested IPMN. A pancreatic resection was performed because of presumed risk of malignancy. Histology revealed pancreatitis and thrombosis of small pancreatic vessels but no IPMN.
The 2 other cases had lesions consistent with IPMN disclosed on MRI. From the first case experience, regular radiography surveillance was decided for both patients. After more than 4 years of follow-up, lesions remained unchanged.
Conclusions. This is the first report of pancreatic lesions suspected to be IPMN finally attributed to ischemic pancreatic duct lesions (sequella of CAPS).
Physicians must be aware that these lesions may be encountered in CAPS and may closely mimic IPMN, with subsequent risk of performing unnecessary pancreatectomy.

Key words: CAPS, pancreatic neoplasms, thrombosis

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PULSE WAVE VELOCITY AS A CARDIOVASCULAR DISEASE RISK FACTOR IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Objective. There is an ample evidence of an increased cardiovascular risk in systemic lupus erythematosus (SLE) that is not justified entirely by traditional cardiovascular risk factors. The pulse wave velocity (PWV), a measure of arterial stiffness, seems to be one of the first changes in these patients being an important predictor of cardiovascular risk. The target of this study is to realize which factors contribute to changes in PWV in patients with lupus, including traditional cardiovascular risk factors, factors related to disease and related to treatment.
Design and Method. A sample of 97 patients (45.4±12.4 years) with SLE took part on the study, being withdrawn information from their medical record (personal history, disease progression, treatment performed to date, analytical data and the presence of other diseases has been withdrawn). The patients were subsequently summoned to collect anthropometric data, applied an index of disease activity, blood pressure measurement and pulse wave velocity by applanation tonometry.
Results. The PWV was 7.015±1,53m/s being the age the biggest influencer of its value (RS=.663, p<.001;R2=0,44). Abdominal obesity in women, obesity, hypertension, dyslipidemia, menopause and family history of cardiovascular risk had impact on arterial stiffness. However, after adjusting for age, only family history of cardiovascular risk and obesity remained as influential factors. Blood pressure, the triglycerides and total cholesterol value also demonstrated impact. Antimalarials were the only drug with a statistically significant impact on arterial stiffness showing a protective effect (Z(U)=-3.076, p=.002).
Conclusions. There should be a control of traditional cardiovascular risk factors whose impact is supported by this study, and the measurement of pulse wave velocity is an option to do that. There is still a need for further research to understand which other factors are responsible for the increased cardiovascular risk in these patients.

Key words: systemic lupus erythematosus, arterial stiffness, pulse wave velocity

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IS THERE PERIPHERAL VASCULOPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS? A VIDEOCAPILLAROSCOPY STUDY

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Objective. Vascular involvement is commonly described in patients with connective tissue disorders, resulting in significant burden reflected by impaired disease outcomes, compromised quality of life, even premature death. While nailfold videocapillaroscopy is extensively used to assess peripheral vasculopathy in patients diagnosed with systemic scleroderma, the capillaroscopic in systemi lupus erythematosus (SLE) is less specific, including a wide range of microvascular changes namely the SLE-type pattern.
The main aim of our study was to evaluate the association between Raynaud's phenomenon (RP) and specific capillaroscopic findings in patients with SLE.
Design and Method. we performed a prospective observational cross-sectional videocapillaroscopic study on 45 SLE patients (fulfilling the 1987 ACR diagnostic criteria) and 45 age- and sex matched healthy volunteers (control group).
SLE patients were classified in two groups according to the presence of RP (19 women with positive RP-SLE group, mean age of 39±15.4 years; 26 SLE without RP, mean age, of 43±17 years). Nailfold videocapillaroscopy was performed using Videocap 200x videocapillaroscope (Optilia). Clinical, laboratory and capillaroscopic findings were analysed using linear and logistic regression, adjusted for age and sex.
Results. Different capillaroscopic changes were reported in our SLE patients, irrespective of the presence of RP, including: dilated (66%) and elongated capillaries (63%), tortuosity (78%), prominent subpapillary plexus (56%), haemorrhages (13.6%) as well as giant capillary loops (4.6%). Moreover, more that half of cases (52%) featured a SLE-type capillaroscopic pattern. However, up to 22% of cases presented with non-specific changes, while in 21% a normal capillaroscopic profile was identified. Surprisingly, 5% of SLE had a scleroderma- like pattern. Subgroup analysis demonstrated significant more enlarged capillaries (p=0.03), avascular areas (p=0.04), capillary hemorrhages (p=0.03), and granular blood flow (p=0.04) in SLE with RP as compared with those without RP. On the other hand, frequency of normal (9 vs. 12%, p=0.30) and nonspecific (13 vs. 9%, p=0.56) capillaroscopy findings were similar in both groups. Scleroderma-like pattern was described only in patients with RP (5 %; p=0.04).
Finally, abnormal total antinuclear antibodies (ANA) were detected in the majority of cases with a SLE-type capillaroscopy pattern (93.3%).
Conclusions. Microvascular abnormalities are commonly detected in SLE patients regardless of the presence of RP, as supported by nailfold videocapillaroscopy.

Key words: systemic lupus erythematosus, nailfold videocapillaroscopy, Raynaud phenomenon

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SUBCLINICAL ATHEROSCLEROSIS IN SLE PATIENTS WITH LOW DISEASE ACTIVITY IS ASSOCIATED WITH BODY MASS INDEX, HDL CHOLESTEROL, AND USAGE OF NSAID AND GLUCOCORTICOIDS

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Objective. Systemic lupus erythematosus (SLE) patients have increased risk of advanced atherosclerosis. While the mechanism is not completely understood, immunologic deterioration and traditional risk factors have been regarded to contribute.
Design and Method. We assessed carotid artery intima-media thickness (cIMT) and plaque by Doppler ultrasonography among 61 female SLE patients enrolled in the study of subclinical atherosclerosis 4 years ago.
Results. The mean cIMT was 0.39±0.09 mm and 11 patients had carotid plaques, which were not different with the previous study. Twenty-one patients had the increased cIMT, and new carotid plaque was developed in 7 patients. The patients with increased cIMT had lower body mass index (BMI), longer disease duration, less commonly took NSAID, and higher cumulative glucocorticoids dose compared with those not. The patients with new carotid plaque development

had lower HDL cholesterol and higher doses of glucocorticoids. On multiple regression analysis, BMI (r=0.62, *p*=0.01), HDL cholesterol (r=0.94, *p*=0.02), and taking NSAID (r=0.16, *p*=0.03) were related with cIMT increment, and current glucocorticoids dose (r=1.14, *p*=0.04) were associated with plaque development.
Conclusions. The follow up study for SLE patients with low disease activity showed low BMI, low HDL cholesterol, and not taking NSAID were associated with cIMT increment. Moreover, current glucocorticoids dose was associated with plaque development. Considered that mean BMI was lower than other studies, obesity paradox in cardiovascular disease risk might support it.

Key words: carotid intima media thickness, low disease activity, body mass index

P7:166

ENDOTHELIAL DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITHOUT PREVIOUS CARDIOVASCULAR EVENTS

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Objective. Cardiovascular disease (CVD) due to premature atherosclerosis is a leading cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE) patients. Early identification of patients with subclinical disease and tight control of cardiovascular risk factors are essential to reduce such complication. Aim of the study was to assess the prevalence of endothelial dysfunction (ED) and related risk factors by a non invasive procedure in SLE patients with early disease without history of CVD.
Design and Method. All the consecutive SLE patients, according to 2012 Classification Criteria, with a disease duration less than 5 years, seen in the Rheumatology and Nephrology Unit of our Hospital from December 2014 to March 2016 were proposed to participate to the study. Exclusion criteria were represented by: history of CVD, diabetes, chronic renal disease (creatinine clearance<60 ml/min), not controlled systemic arterial hypertension, current smoking or smoking in the last 3 years, hypercholesterolemia (total cholesterol>240 mg/dl), obesity (body mass index > or =30), statin or beta-blocker use. Each patient underwent a clinical and serological evaluation, a transthoracic Doppler echocardiogram and an evaluation of endothelial function by endoPAT technique. Characteristics of patients with ED, defined as reactive hyperemic index < or= 2, were compared to those of patients without ED by Fisher, T student or Mann-Whitney tests as appropriate.

Table I. Disease characteristics and treatment of 20 SLE patients included in the study.

Variable	Value
Cutaneous, n (%)	11/20 (55%)
Mucosal, n (%)	5/20 (25%)
Renal, n (%)	8/20 (40%)
Articular, n (%)	14/20 (70%)
Neurological, n (%)	1/20 (5%)
Serositic, n (%)	5/20 (25%)
Hematological, n (%)	13/20 (65%)
Antiphospholipid Syndrome, n (%)	1/20 (5%)
Antinuclear antibody positivity, n (%)	20/20 (100%)
Anti-double stranded DNA positivity, n (%)	10/20 (50%)
Anti-extractable nuclear antigen positivity, n (%)	12/20 (60%)
Anti-cardiolipin IgG positivity, n (%)	1/20 (5%)
Anti-cardiolipin IgM positivity, n (%)	4/20 (20%)
Antiβ2Glycoprotein I IgG positivity, n (%)	2/19 (10%)
Antib2Glycoprotein I IgM positivity, n (%)	2/19 (10%)
Lupus anticoagulant positivity, n (%)	5/19 (26%)
C3 mg/dL, mean (SD)	86 (19)
C4 mg/dL, mean (SD)	14 (7)
Systemic Lupus Erythematosus Disease Activity Index 2K, mean (SD)*	4 (3)
Systemic Lupus International Collaborating Clinics Damage Index, mean (SD)	0.5 (0.9)
Steroids, n (%)	19/0 (95%)
Antimalaric, n (%)	18/20 (90%)
Disease Modifying Antirheumatic Drugs, n (%)	11/20 (55%)
Belimumab, n (%)	1/20 (5%)
Intravenous Immunoglobulin, n (%)	1/20 (5%)
Low dose aspirin, n (%)	8/20 (40%)
Oral anticoagulant, n (%)	2/20 (10%)
Anti-hypertensive drugs, n (%)	8/20 (40%)

*measurable in 19 patients; °measurable in 14 patients.

Results. Among 46 screened SLE patients, 19 (41%) were excluded for one or more exclusion criteria and 7 (15%) refused. We enrolled 20 patients (100% female, 80% caucasian) with a median disease duration of 14 months (0-68), a mean age of 42 years (±15), and a mean age at diagnosis of 40 years (±16). Five patients (25%) had a systemic hypertension that was well controlled by treatment. No other cardiovascular risk factors were present. Disease characteristics and treatment are shown in Table I. Echocardiogram showed diastolic dysfunction in 5 patients (25%). EndoPAT identified 8 patients (40%) with ED. We did not find any significant association between the presence of ED and demographic-clinical-serological-echocardiographic characteristics of patients or treatments (data not shown).
Conclusions. A significant proportion of SLE patients showed signs of ED despite a recent disease and the absence of significant cardiovascular risk factors.

Key words: systemic lupus erythematosus, endothelial dysfunction, diastolic dysfunction

P7:167

PRECLINICAL VASCULAR DAMAGE IN PREMENOPAUSAL SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND IN CONTROLS; ARE THERE ANY DIFFERENCES ?

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Objective. In patients with Systemic lupus erythematosus (SLE) a greater prevalence of structural and functional vascular alterations has been described, possibly explaining the higher incidence of cardiovascular events, as compared to subjects matched for age and sex.
Aim of this study was to analyze the presence of target organ damage in premenopausal women with SLE (LES), in controls matched for age and sex (control 1) and in an additional control group of women matched for demographic characteristics and also for other cardiovascular risk factors (control 2).
Design and Method. 33 patients with SLE clinically stable (SLEDAI Score 2.5±1.5) (mean age 32±7 years, range 19-44), 17 controls matched for age and sex and 33 controls matched for sex, age, body mass index (BMI), clinic blood pressure (BP) and antihypertensive treatment (if present), underwent: 24 hours BP monitoring, carotid ultrasound for intima-media thickness (IMT) measurement, and pulse wave velocity measurement for aortic stiffness (PWV).
Results. By definition no difference was observed for age, sex, BMI and clinic BP values and a similar Framingham risk score between SLE and control 2 patients (1.3±2.7 vs 1.5±2.3%, *p*=ns). SLE patients had lower BMI and greater BP values, both clinic and 24 hours (see table 1) as compared to control 1. IMT was significantly greater in SLE as compared to control 1, while no differences in PWV were observed among the 3 groups (see Table I). At logistic regression analysis, PWV was independently associated with the steroid weekly dose in SLE patients.
Conclusions. In patients with SLE and low activity index of the disease we observed greater clinical and 24 hours BP values and IMT as compared to "healthy" age- and sex- matched controls, but not more severe vascular alterations as compared to controls with similar cardiovascular risk.

	Control 1	Control 2	SLE
BMI (kg/m^2)	20.3±2.0	23.0±4.1*	23.0±4.5*
Clinic SBP (mmHg)	103±7	114±13*	114±10*
Clinic DBP (mmHg)	64±6	73±12*	70±9
24 hours SBP (mmHg)	105±5	117±9*	115±10*
24 hours DBP (mmHg)	65±5	74±7*	73±10*
24 hours HR (bpm)	75±8	75±9	81±9*§
PWV (m/s)	6.65±1.04	6.98±0.73	6.77±0.80
IMT (mm)	0.65±0.1	0.69±0.1	0.72±0.1*

Anova, p at least <0.05 vs *Control 1, §Control 2.

Key words: preclinical vascular damage, intima-media thickness, pulse wave velocity

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IS HYPERURICEMIA AN INDEPENDENT RISK FACTOR FOR ARTERIAL THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS?

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Objective. To evaluate whether hyperuricemia is independently associated with cardiovascular events in a cross-sectional study of Chinese patients with SLE.
Design and Method. Consecutive patients who fulfilled ACR criteria for SLE were studied. Fasting blood was taken for urate level, glucose and lipid profile. Patients were assessed for body mass index (BMI), waist circumference and the presence of the metabolic syndrome (MetS) as defined by the updated joint consensus criteria, using the Asian criteria for central obesity. Patients were stratified according to different serum urate levels. Comparison of the prevalence of vascular risk factors, the MetS and arterial thrombotic events was made among these groups. Cox regression models were established to study if hyperuricemia was independently associated with arterial events with adjustment for confounding variables.
Results. 485 SLE patients were studied (93% women; age 46.2±14 years); 73 (15%) had chronic kidney disease stage 3 or more. Hyperuricemia (urate >0.35mmol/L) was present in 38% patients. The number of patients who had serum urate levels of 0.35-0.48, 0.48-0.60 and >0.60mmmol/L was 131 (27%), 40 (8.7%) and 14 (2.9%), respectively. Patients with hyperuricemia were more likely to be men (14% vs 3%; p<0.001), have renal disease (72% vs 42%; p<0.001), hypertension (34% vs 15%; p<0.001), lower eGFR (73.4±34 vs 101±27; p<0.001) but longer SLE duration (14.3±8.7 vs 12.1±7.4 years; p=0.006). The LDL-cholesterol (3.34±1.37 vs 2.89±1.51mmol/L; p=0.001), triglyceride (1.62±0.77 vs 1.29±0.78mmol/L; p<0.001), body mass index (BMI) (23.2±4.5 vs 22.3±3.8kg/m2; p=0.04) and occurrence of the MetS (22% vs 12%; p=0.007) were significantly higher in hyperuricemic patients. On the contrary, patients with the MetS had significantly higher serum urate levels than those without (0.38±0.11 vs 0.34±0.13mmol/L; p=0.007). Over an observation of 12.9±8.0 years, 50 acute arterial events (17 acute coronary syndrome; 24 stroke, 7 peripheral vascular event and 2 retinal artery thrombosis) developed in 47 patients. The cumulative risk of arterial thrombosis was 5.2% and 6.4% in 10 and 15 years, respectively. Acute coronary events were significantly more common in patients with hyperuricemia than those without (7.6% vs 1.0%; p=0.001). Cox regression analysis revealed that HDL<1.0mmol/L (HR 3.44[1.62-7.27]; p=0.001], lupus anticoagulant (HR 3.84[1.92-7.65]; p<0.001) and age of SLE onset (1.03[1.004-1.05] per year; p=0.02) were independently associated with arterial thrombosis. In separate regression models, elevated urate levels (>0.35, >0.48 or >0.60mmol/L) were not significantly associated with arterial events after adjustment for age, sex, eGFR, smoking, LDL-cholesterol, HDL-cholesterol, triglyceride, BMI, diabetes mellitus, hypertension and the antiphospholipid antibodies.
Conclusions. Hyperuricemia was associated with renal dysfunction, MetS and acute coronary events in patients with SLE. However, in multivariate analyses, hyperuricemia was not an independent risk factor for acute coronary or any arterial events after adjustment for confounding factors.

Key words: lupus, hyperuricemia, cardiovascular

P7:169

41 CASES OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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Objective. The antiphospholipid antibody syndrome (APS) is characterized by the occurrence of thrombotic events and/or gestational morbidity in the presence of antiphospholipid antibodies in the serum. It can manifest as a primary disorder or be secondary to other diseases, more frequently systemic erythematous lupus (SLE). It has a varied clinical spectrum, as thrombotic phenomena can occur in all kinds of vascular territories (arterial, venous and small vessels). It is more frequent in the female population and tendentiously in a young age. Our aim is to present and characterize the 41 cases diagnosed with APS followed in the Autoimmune Diseases Department of Hospital Santo António dos Capuchos.
Design and Method. Patients diagnosed with APS were selected from the Autoimmune Diseases Department registry of Hospital Santo António dos Capuchos. Clinical and demographic information was obtained retrospectively from clinical records.
Results. 77% of all cases are female and 23% male. 58% are primary and 42% secondary. From those 77% are SLE related. The mean age at presentation was 42 years old. Regarding clinical manifestations, the more frequent were deep vein thrombosis, stroke and pulmonary embolism, although we have observed a large spectrum of clinical manifestations, such as intra-abdominal thrombosis, retinal ischemia, intra-cardiac thrombus, livedo reticularis, thrombocytopenia, among others. The serologic findings included 60% of all cases positive for Lupus anticoagulant and regarding autoantibodies, anticardiolipin was positive in 46% and beta-2 glycoprotein in 40% of all cases. 31% were positive for more than one autoantibody. The vast majority of them is under oral anticoagulation, and only one is under no therapeutics.
Conclusions. This work allowed us to characterize the main clinical and immunological manifestations of our population diagnosed with APS. Our data are similar to the ones reported in a large European cohort.

Key words: antiphospholipid syndrome, lupus related, cohort

P7:170

ECHOCARDIOGRAM FINDINGS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. The aim of this study was to identify cardiac abnormalities in asymptomatic systemic lupus erythematosus (SLE) patients and to investigate their association with disease characteristics.
Design and Method. This is a prospective cross-sectional study. SLE patients who attended rheumatology clinics were evaluated with a detailed clinical history, physical examination and laboratory investigations. Transthoracic Echocardiogram (TTE) was done for all patients. Chi-square / Fisher's exact test was used to determine the significant relationship among categorical variables. All data was entered and analyzed through statistical package SPSS version 22.
Results. 50 patients (46 female, 4 male) with disease duration 53.6±35.9 months. 52% patients have anti-DNA and 30.6% have antiphospholipid antibodies.
TEE studies revealed 32.7%, 18%, 10.2% of our patients had mitral, tricuspid and aortic regurgitations respectively. 32% of our patients had pericardial effusion.Non of our patients had stenotic valve.
Positive anti-DNA antibody was associated with mitral and tricuspid valve regurgitations but not with aortic valve (Table I, II).

Table I		Mitral valve abnormalities No	Yes	p value
Age	12-20	3 (9.4%)	4 (25.0%)	0.121
	21-30	12 (37.5%)	9 (56.3%)	
	31-40	5 (15.6.%)	3 (15.5%)	
	41-50	8 (25.0%)	0 (0.0%)	
	51-60	3 (9.4%)	0 (0.0%)	
	>60	1 (3.1%)	0 (0.0%)	
Gender	Female	30 (90.9%)	15 (93.8%)	0.733
	Male	3 (9.1%)	1 (6.3%)	
HTN	No	28 (84.8%)	12 (75.0%)	0.404
	Yes	5 (15.2%)	4 (25.0%)	
DM	No	31 (93.9%)	15 (93.8%)	0.979
	Yes	2 (6.1%)	1 (6.3%)	
Hydroxylchloroquine	No	1 (3.0%)	1 (6.3%)	0.593
	Yes	32 (97.0%)	15 (93.8%)	
Azathioprine	No	18 (54.5%)	11 (68.8%)	0.343
	Yes	15 (45.5%)	5 (31.3%)	
(MMF) Cellcept	No	20 (60.6%)	9 (56.3%)	0.771
	Yes	13 (39.4%)	7 (43.8%)	
Cyclophosphamide	No	26 (78.8%)	12 (75.0%)	0.766
	Yes	7 (21.2%)	4 (25.0%)	
Prednisolone	No	4 (12.1%)	2 (12.5%)	0.97
	Yes	29 (87.9%)	14 (87.5%)	
C3	Normal	14 (42.4%)	5 (31.3%)	0.452
	Low	19 (57.6%)	11 (68.8%)	
C4	Normal	25 (75.8%)	11 (68.8%)	0.602
	Low	8 (24.2%)	5 (31.3%)	
ANA	Negative	4 (12.5%)	5 (31.3%)	0.117
	Positive	28 (87.5%)	11 (68.8%)	
Anti-ds DNA (at the time of echo)	Negative	19 (61.3%)	4 (25.0%)	*0.018
	Positive	12 (38.7%)	12 (75.0%)	

Table II

		Tricuspid valve		*p*-value
		No	Yes	
Age	12-20	4 (10.5%)	3 (30.0%)	0.575
	21-30	18 (47.4%)	3 (30.0%)	
	31-40	6 (15.8%)	2 (20.0%)	
	41-50	6 (15.8%)	2 (20.0%)	
	51-60	3 (7.9%)	0 (0.0%)	
	>60	1 (2.6%)	0 (0.0%)	
Gender	Female	35 (59.7%)	10 (100.0%)	0.291
	Male	4 (10.3%)	0 (0.0%)	
HTN	No	32 (82.1%)	8 (80.0%)	0.881
	Yes	7 (17.9%)	2 (20.0%)	
DM	No	37 (94.9%)	9 (90.0%)	0.366
	Yes	2 (5.1%)	1 (10.0%)	
Hydroxylchloroquine	No	2 (5.1%)	0 (0.0%)	0.463
	Yes	37 (94.9%)	10 (100.0%)	
Azathioprine	No	25 (64.1%)	4 (40.0%)	0.167
	Yes	14 (35.9%)	6 (60.0%)	
(MMF) Cellcept	No	24 (61.5%)	5 (50.0%)	0.503
	Yes	15 (38.5%)	5 (50.0%)	
Cyclophosphamide	No	31 (79.5%)	7 (70.0%)	0.521
	Yes	8 (20.5%)	3 (30.0%)	
Prednisolone	No	6 (15.4%)	0 (0.%)	0.185
	Yes	33 (84.6%)	10 (100.0%)	
C3	Normal	15 (33.5%)	4 (40.0%)	0.929
	Low	24 (61.5%)	6 (60.0%)	
C4	Normal	29 (74.4%)	7 (70.0%)	0.781
	Low	10 (25.6%)	3 (30.0%)	
ANA	Negative	8 (21.1%)	1 (10.0%)	0.426
	Positive	30 (78.9%)	9 (90.0%)	
Anti.ds DNA (at the time of echo	Negative	22 (59.5%)	1 (10.0%)	*0.006

Conclusions. Positive anti-DNA antibody was observed in 52% of SLE patients and was associated with mitral and tricuspid regurgitations. Serological active disease may predispose SLE patients to valvular heart disease. Regular TEE is important to identify the structural heart disease in asymptomatic SLE patients.

Key words: systemic lupus erythematosus, echocardiogram, cardiac dysfunction

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A STUDY OF THE CARDIOVASCULAR DISEASE RISK FACTORS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To study the cardiovascular disease risk factors in patients with Systemic Lupus Erythematosus (SLE).
Design and Method. 170 patients with SLE were evaluated during the study. 58 out of 170 were male (34.12%) and 112 women (65.88%), between 20 and 85 years of age. They all met the criteria of the American College of Rheumatology.30 serum samples from people who were similar to the group of patients as far as the age and gender are concerned, were the control group. The fasting blood glucose levels as well as the cholesterol levels, the triglyceride levels, and the levels of HDL and LDH were assayed by an automated biochemical analyzer and the decennial cardiovascular disease risk was calculated.
Results. There was a statistically significant variation between the patients of the control group as far as the triglyceride levels are concerned. The incidence of hypertriglyceridemia in the group of patients was 40% while in the control group 15% ($p<0.001$). In addition, the incidence of arterial hypertension was statistically significant in the group of patients (45%) compared to that in the control group (10%) as well as the levels of HDL which were lower in the group of patients (45.3 mg/dl versus 38 mg/dl $p<0.05$).
Conclusions. Our findings comply with the ones referred in international and domestic bibliography and verify that the most significant risk factors in patients with SEL are arterial hypertension and dyslipidemia.

Key words: dyslipidemia, arterial hypertension, HDL

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UNDIAGNOSED ANTIPHOSPHOLIPID SYNDROME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CLINICAL IMPLICATIONS – A CASE REPORT

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Objective. Antiphospholipid syndrome (APS) is frequently associated with Systemic lupus erythematosus (SLE). However, due to common organ involvements like kidney failure or alveolar haemorrhage (1), APS diagnosis is often not timely formulated in SLE patients, inducing a severe clinical outcome in this subset of patients. In fact underlying pathogenetic mechanisms in APS and SLE are different and consequently treatments should be differentiated
Design and Method. We report a case of a 47-year old male who was diagnosed with SLE in 1995, based on antinuclear antibodies (ANA) low positivity (titre 1:160), anti-dsDNA 50 UI/L and on membranoproliferative glomerulonephritis at renal biopsy. Despite treatment with oral steroids (prednisone 1 mg/kg) and then pulse cyclophosphamide, renal function deteriorated to end stage renal disease (ESRD), requiring haemodialysis in 2005. IgG anticardiolipin (aCL) antibodies were firstly detected at high titre in 1995, while anti-beta2 glycoprotein I (aB2 GPI) and lupus anticoagulant (LAC) in 2008 and 2009, respectively. First vascular event was thrombosis of arteriovenous fistula in 2005, followed by two transient ischemic attacks and haemorrhagic alveolitis in 2008. During this period the patient was treated with steroids and mycophenolate. One year later the patient underwent to replacement of aortic valve for severe aortic regurgitation. During the postoperative period an acute myocardial infarction occurred, without evidence of epicardial coronary stenoses at coronary angiography. In order to prevent mechanic valve thrombosis, anticoagulation therapy (warfarin) was introduced but, due to a bad patient's compliance, at a low level of INR, mostly below 2.0. Subsequently, between 2012 to 2013, a new arteriovenous fistula thrombosis occured along with several necrotic lesions in the fingers and toes, requiring amputations of four toes and one finger.
Results. At admission to our hospital in October 2013 the patient showed multiple painful, ischemic and necrotic lesions at both hand fingers and both feet toes. Microbiological swabs were positive for Pseudomonas aeruginosa and Escherichia Coli. In our laboratory autoantibody assays revealed ANA positive at high titre with homogenous pattern, aCL and aB2 GPI antibodies both high titre, and lupus anticoagulant (LAC) positivity, while anti-Sm and anti-dsDNA antibodies were absent. According to the Sidney classification criteria, diagnosis of APS was stated. Oral anticoagulation was increased, with an INR between 2.5-3.5, and antiplatelet therapy was introduced along with targeted antibiotic therapy. Moreover, considering the patient's severe clinical condition, triple therapy (plasma exchange, intravenous immunoglobulins and steroids) usually recommended in catastrophic APS was started without any benefit. In fact ischemic lesions increased requiring amputation of the right lower limb. The patients died one year later for sepsis.
Conclusions. this case report suggests that APS should be diagnosed early in SLE patients in order to timely provide the correct treatment so avoiding a poor outcome.

Reference

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Key words: antiphospholipid syndrome, systemic lupus erythematosus, diagnosis

Poster session 8: Challenges in management of SLE (1)

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THE CRETAN LUPUS REGISTRY "LETO": INCIDENCE AND PREVALENCE OVER A 15-YEAR PERIOD, CLINICAL FEATURES AND ENVIRONMENTAL FACTORS IN A HOMOGENEOUS, SOUTHERN-EUROPEAN POPULATION

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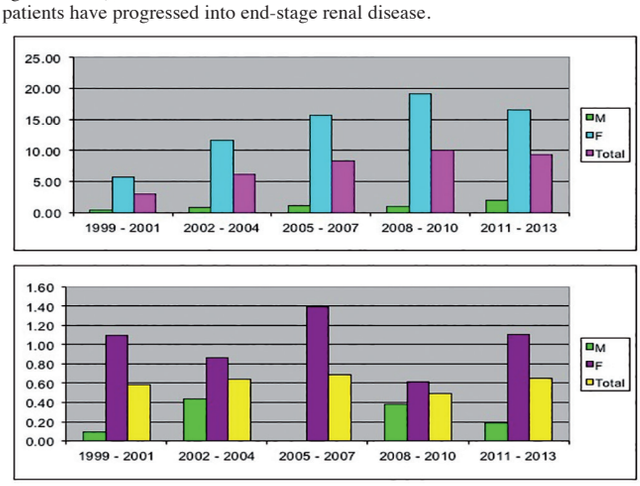
Objective. Crete is the third largest southernmost Mediterranean island with a relative isolated geographically population of approximately 0.6M inhabitants. We sought to: i) to estimate the prevalence and incidence of SLE in Crete over the period of 1999-2013, including temporal trends, variation with age, gender and residency; and ii) to describe the clinical burden at the community level.
Design and Method. An electronic platform surveillance methodology system was employed with multisource case finding and comprehensive data synthesis. SLE cases fulfilling the ACR 1997 classification criteria (primary definition), with physician-based diagnosis (secondary definition), or fulfilling the SLICC 2012 criteria (third definition), aged above 14 years and residing in Crete were included. Direct standardization by age and gender was performed using the European Standard Population.
Results. Using the primary case definition, the overall crude and age-adjusted incidence rate of SLE in Crete was 8.7 (95% confidence interval [CI] 8.1-9.4) and 7.4 (95% CI 6.8-7.9) per 100,000 inhabitants/year, respectively. The point prevalence (December 2013) was 152 per 100,000 people (total 799 patients). Following previous decade increasing trends, SLE incidence rates appear to have plateaued since 2007, with physician-based diagnosis showing slightly higher rates compared to classification-based. The average age at the time of diagnosis is 43 (± 15) years (range 9-81) with female:male ratio of 13:1. Patients were classified according to BILAG system as having mild (50%), moderate (33%) and severe (17%) disease. 104 patients (13%) had biopsy-proven lupus nephritis (LN) corresponding to a crude prevalence 20 per 100,000 inhabitants. LN incidence trends remained stable during the 15-year period. Primary neuropsychiatric lupus was diagnosed in 46 patients corresponding to 7% of SLE cases. After follow-up of 8 (± 7) years, 37% of patients have accrued organ damage (SLICC/ACR damage index >0), with increased rates in rural versus urban residents, and 8% of LN patients have progressed into end-stage renal disease.



SLE Incidence (a) and SLE nephritis in Crete, Greece 1999.2013 (age adjusted rates).

Conclusions. By employing a comprehensive, unbiased surveillance/population based methodology we found that SLE occurrence in Crete, Greece may be higher than previously reported in Northern European regions. Our results suggest an increased ratio of mild versus severe forms of SLE in the community as opposed to tertiary settings, although possible effects of environmental factors on the disease phenotype cannot be excluded. These data may help in the optimization of public health surveillance and policies.

Key words: nephritis, classification criteria, disease severity

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DIAGNOSTIC CHALLENGE OF DIFFERENT NEUROPSYCHIATRIC LUPUS MANIFESTATIONS: PERFORMANCE OF AN ATTRIBUTION ALGORITHM IN THIS WIDE SPECTRUM DISORDER

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Objective. A recently developed algorithm, based on a numerical score (range 0-10), to determine the attribution of neuropsychiatric (NP) events to SLE or other causes has been preliminary validated.
Aim. To test the performance of the attribution algorithm for different NP manifestations in a multicenter international cohort of SLE patients, all of whom had one or more NP events, as per the 1999 ACR case definitions.
Design and Method. A large retrospective multicentre international cohort was recruited from eleven academic rheumatology centres in 5 countries. Patients from each centre satisfied ACR classification criteria for SLE and had one or more NP event(s). A dedicated electronic chart was created, to record a core set of items for classification. Four factors were considered for each NP event (i) the time of onset of the NP event; (ii) the presence of concurrent or confounding non-SLE factors (*i.e.* "associations" suggested in the glossary for the 1999 ACR case definitions); (iii) the type of NP event (major/rare vs minor/frequent) according to Ainiala *et al.*; (iv) the presence of "favouring factors" (*i.e.* supporting attribution). The performance of the attribution score of the first NP event was compared to that determined by clinical judgement, assumed as the "gold standard". Receiver Operating Curve (ROC) analysis was used to determine the area under the curve (AUC) using dichotomous outcomes (related vs uncertain/not related to SLE). Accuracy of the algorithm was evaluated according to the following scale: .91-1 = excellent, .81-.90 = good, .71-.80 = fair, .61-.70 = poor, < .61 = fail.
Results. A total of 668 patients (52 M, 616 F); mean (SD) age at first NP event 38.3 years (13.6) were included. The performance of the attribution algorithm was analysed only for those NP events for which a sample of at least 10 cases was available (12 of the 19 case definitions) and the results are summarized in Table I.

Table I

NPSLE	N* of case observed	%	AUC	95%CI
All events	614	100	0.83	0.80-0.86
Central NPSLE	**N* of case observed**	**%**	**AUC**	**95%CI**
Headache	163	24.33	0.79	0.72-0.86
Mood disorder	104	15.52	0.74	0.63-0.84
Cerebrovascular disease	94	14	0.83	0.73-0.92
Seizure disorders	60	8.96	0.92	0.08-1.00
Cognitive dysfunction	40	5.97	0.71	0.52-0.88
Anxiety disorder	40	6.97	0.68	0.49-8.87
Psychosis	31	4.63	0.98	0.97-1.00
Demyelinating syndrome	13	1.94	0.89	0.75-1.00
Peripheral NPSLE	**N* of case observed**	**%**	**ROC area**	**95%CI**
Polyneuropathy	24	3.58	0.63	0.40-0.86
Cranial neuropathy	21	3.13	0.86	0.64-1.00
Myastenia gravis	13	1.94	0.65	0.14-1.00
Mononeuropathy	11	1.64	0.89	0.75-1.00

(*when >10 cases).

Conclusions. In this large and well characterized multicentre international cohort of SLE patients with NP involvement the accuracy of the attribution algorithm was variable with a good/excellent performance for psychosis and seizure disorders. Future studies are needed to enhance performance for other NP events.

Key words: systemic lupus erythematosus, neuropsychiatric SLE, attribution algorithm

Table I. (P8:178)

DESCRIPTIVES OF STUDY COHORT	
Number of study patients (n)	100
Age (mean ± SD) years	44.4±14.7
Gender:	
Female (%)	91
Ethnicity:	
African American (%)	46
Caucasian (%)	29
Asian (%)	5
Hispanic (%)	17
Other (%)	2
Less than High School (%)	2
Education:	
Less than High School (%)	2
High School (%)	34
College/University degree (%)	49
Graduate degree/Higher (%)	15
Insurance:	
HMO (%)	3
PPO (%)	37
Medicaid (%)	18
Medicare (%)	22
Other (%)	18
Charity care (%)	1
No Coverage (%)	1
Primary Care Physician:	
Yes	93
Disease Duration (mean ± SD) years	8.6±6.9
Number of ACR criteria met (mean ± SD)	5.2±1.4
Frequency of ACR criteria met:	
Malar Rash (%)	57
Discoid Rash (%)	18
Photosensitivity (%)	41
Oral ulcers (%)	41
Arthritis (%)	80
Serositis (%)	33
Renal disorder (%)	24
Class 1 - Minimal mesangial (%)	0
Class 2 - Mesangial proliferative (%)	1
Class 3 - Focal proliferative (%)	9
Class 4 - Diffuse proliferative (%)	3
Class 5 - Membranous (%)	10
Class 6 - Sclerosing (%)	1
Neurological disordder (%)	9
Hematological disorder (%)	37
Immunologic disorder (%)	87
ANA*(%)	9
PGA (median; IQR)	0.2;0.4
SLEDAI-SELENA (median; IQR)	2;4
SDI (median; IQR)	0;1
Medications:	
Steroids- ever (%)	80
Steroids- current (%)	38
Steroids Dose (median; IQR)	10;15
Hydroxychloroquine (%)	88
Methotrexate (%)	16
Azathioprine (%)	15
Mycophenolate mofetil (%)	22
Other medications** (%)	11

Table II.

PERFORMANCE ON QUALITY INDICATORS (Qs)

Qs No.	Descriptions of Qs	No of patients eligible for Qs (N)	No of patients who met Qs (n)	Performance percentage (%)	Deficiency
1	ANA, CB, Platelet. Creatinine, UA at diagnosis of lupus	100	99	94.0	UA (nº=1)
2	AntidsDNA, C3/4, APL within 6 months of diagnosis	100	54	54.0	APL (nº=46) AntidsDNA (no=1)
3	Counselling for use of sunscreen	100	94	94.0	
4	Influenza vaccine in last year if on ISM	61	56	92.0	
5	Pneumococcal vaccine if on ISM	61	44	72.0	
6	DEXA if have received ≥7.5 mg/day CS for ≥3 months	67	52	77.6	
7	Calcium and Vitamin D if have received ≥7.5 mg/d CS for ≥3 months or is post-menopausal	76	60	78.9	
8	Antiresorptive agent if have received ≥7.5 mg/d CS for ≥1 month & central T score ≤2.5 or h/o fragility fracture	13	13	100.0	
8	Counselling about drugs at initiation	100	90	90.0	
10	Baseline tests at initiation of drugs	99	96	97.0	Fundus (HCQ)(nº=3)
11	Tests for drug monitoring	97	86	88.7	Fundus (HCQ) (nº=8) Labs (MTX) (nº=1) Labs (MMF) (nº=2)
12	Initiation of steroid sparing agents if have taken ≥10 mg/d CS for ≥3 months	60	56	93.3	
13	Follow-up tests (UA, C8C, Creatinine) done for LN at every 3 months	24	17	70.8	UA (nº=2) All not done every 3 months (nº=5)
14	Treatment with ISM & CS within 1 months of diagnosis of Class 3/4 LN	20	20	100.0	
15	Antihypertensive if have proteinuria ≥300 mg/d or GFR <60 ml/min & ≥2 BP readings > 130/80	23	22	95.7	
16	ACE inhibitors or ARB if have proteinuria ≥300 mg/d	2	2	18	81.8
17	Assessment of CVD risk & counselling	100	26	26.0	Lipid (nº=64) Counselling (nº=43)
18	Tests related to pregnancy (AntiSSA/SSB, APL)	14	8	57.0	AntiSSA/SSB (nº=3) APL (nº=3)
19	Treatment of APS in future pregnancies	2	2	100.0	
20	Reproductive health counselling	36	30	83.3	

ANA: Antinuclear antibody; CBC: Complete Blood Count; UA: Urinalys; APL: Antiphospholipid antibodies; ISM: Immunosuppressive medications; CS: Corticosteroid; HCQ: Hydroxychloroquine; MTX: Methotrexate.

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INFLAMMATORY BACK PAIN IS INCREASED IN SLE; A LONGITUDINAL COHORT STUDY

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Objective. To determine the frequency of inflammatory back pain (IBP) in systemic lupus erythematosus and the association with autoantibodies.
Design and Method. Presence of low back pain (LBP) was questioned in 132 patients with SLE and 100 healthy controls (HC). Then a questionnaire containing 5 questions relating inflammatory back pain (IBP) according to ASAS-IBP criteria was conducted to all. Patients who had back pain in first evaluation were evaluated again after 5 years. A rheumatologist and a radiologist blinded for the patients and controls examined the conventional X-rays and magnetic resonance images (MRI) of sacroiliac joints
Results. In first evaluation, we noticed 58 SLE patients (58/132; 43.9%) with LBP. Among these patients, 22 had inflammatory back pain according to the questionnaire (38% of LBP-SLE; 16.7% of all SLE). This was significantly different than that was seen in HC (22/58 vs. 0/15; $p<0.001$). Within 44 patients who accepted to have a radiologic assessment, 13 (29.5%) had sacroiliitis (9.8% of all SLE) on X-ray. Moreover, a significant association was observed between presence of sacroiliitis and anti Sm antibodies ($p=0.026$).
We could reach 35 patients for second evaluation. Twenty-four (68.5%) patients had still low back pain; 11 (31.4%) were IBP. Eight patients who had IBP were evaluated by MRI imaging and active or chronic sacroiliitis verified in all.
Conclusions. Sacroiliitis is neither rare nor associated with HLA-B27 in SLE. The relationship between IBP and anti-Sm antibodies needs further evaluation.

Key words: sacroiliitis, inflammatory back pain, SLE

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HOW GOOD A CARE ARE WE REALLY PROVIDING TO OUR LUPUS PATIENTS?

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Objective. Knowledge of physician performance on disease specific quality of care measures can provide an opportunity to improve our clinical care processes and patient health outcomes. Herein, we evaluated our quality of care among Systemic Lupus Erythematosus (SLE) patients using SLE quality indicators (QI)[1].
Design and Method. 100 consecutive patients receiving longitudinal care at the Rush University Rheumatology outpatient clinic were recruited. Inclusion criteria were fulfillment of the American College of Rheumatology classification criteria for SLE, and an informed consent. A validated QI survey[1] was updated (removal of QI requiring chest imaging prior to start of methotrexate), modified for self-report and administered during participants' routine SLE care visit. Retrospective rheumatology medical chart reviews were done in addition for complete evaluation of each QI performance. Descriptive analyses were performed. Performance rates for 20 individual QIs were calculated using "QI met" as numerator and "eligibility for each QI" as denominator. We also calculated the overall performance rate by dividing total number of QIs met by total number of QIs that the participants were eligible for.
Results. Mean (SD) age was 44.4 (14.7) years (Table I). The overall performance rate was 82.6% (IQR: 21%). The performance rate of individual QIs varied between 26% and 100% (Table II). Areas of low performance included assessment and counselling for cardiovascular disease (CVD) risk [Performance percentage (PP): 26%], testing for antiphospholipid (APL) antibodies within 6 months of diagnosis of SLE (PP: 54%), testing for anti-SSA/B and APL antibodies before pregnancy (PP: 57%), laboratory monitoring for active lupus nephritis (LN) among LN patients (PP: 70.8%), and recommendation for pneumococcal vaccine in patients on immunosuppressive medications (ISM) (PP: 72%).
Conclusions. Gaps in performance of SLE specific quality measures were noted among patients receiving longitudinal care for SLE from rheumatologists in a University clinic. While not all of the quality measures are universally accepted, education of rheumatologists and patients with special focus on the importance of preventive care (CVD risk assessment and counselling and vaccination) is indicated.

Reference

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Key words: lupus, quality indicators, performance

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CLINICAL AND SEROLOGICAL DIFFERENCES OF DISEASE EXPRESSION IN LATE ONSET SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS FROM A PORTUGUESE COHORT

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Objective. Systemic lupus erythematosus (SLE) can occur at any age, being more common in females in childbearing age; however around 15% have its onset after the age of 50. Patients with late-onset SLE (LSLE) tend to show more insidious onset and mild initial clinical manifestations. The aim of this study was to characterize and compare demographic, clinical and laboratory data among patients with SLE onset before and after 50 years.
Design and Method. Retrospective study including patients with SLE diagnosis followed at in our centre. The data was obtained by consulting patients' clinical records. The statistical analysis was performed using SPSS 23.0 software, and $p<0.05$ was taken to indicate statistical significance. To compare the differences between the groups, student-t test, Mann-Whitney U, Chi-square and Fisher tests were used.
Results. 204 patients were included, 187 (91.7%) females, with a mean age of 46.1±15.4 years. 17 (8.7%) patients had LSLE, with a female to male ratio of 7:1.5. Disease duration was significantly lower in LSLE patients (12.9±10.6 vs 17.4±9.9 years, $p=0.04$) and the time to diagnosis was longer in LSLE patients, however this latter difference was not statistically significant (2.1±7.3 vs 0.9±2.6 years, $p=0.34$). Leukopenia was significantly more frequent in patients with LSLE (52.9% vs 16.6% $p=0.001$); lymphopenia was also more frequent in these patients but not statistically significant (12.0% vs 9.1%, $p=0.66$). Renal and neuropsychiatric involvement were less frequent in LSLE, however without achieving statistical significance (29.4% vs 41.2%, $p=0.44$ and 0% vs 7.0%, $p=0.60$, respectively). In what concerns immunology, anti-SSA and anti-SSB antibodies were more frequent in LSLE (50.5% vs 29.4% $p=0.01$ and 35.3% vs 10.7% $p=0.001$ respectively) and anti-ribosomal P protein antibodies were less frequent (0% vs 5.1%, $p<0.001$). There were no statistically significant differences in other clinical or serological features, disease activity and damage scores.
Conclusions. Our study showed that SLE patients presenting after 50 years old have some differences in what concerns clinical and serological manifestations.

Key words: late onset lupus, clinical manifestations, immunological manifestions

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SERUM URIC ACID AS A PROGNOSTIC FACTOR OF PULMONARY HYPERTENSION: SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective. To analyze the literature regarding the effect of serum uric acid (UA) on the severity of pulmonary hypertension (PH).
Design and Method. We searched MEDLINE, EMBASE, the Cochrane library, and KoreaMed for all articles published before November 2015. Studies with quantitative data on effect of serum UA on PH were included.
Results. A total of 2,283 subjects were included in 21 studies, including 1,352 subjects with PH and 931 non-PH subjects. Meta-analysis demonstrated that serum UA was significantly higher in the subjects with PH than the non-PH subjects [7 studies, 1,191 subjects, 1.72 mg/dl, $p<0.00001$]. Subgroup analyses by type of underlying diseases showed that the subjects with PH had significantly higher serum UA than the non-PH subjects for systemic lupus erythematosus (2.70 mg/dl, $p=0.00001$), systemic sclerosis (1.16 mg/dl, $p<0.00001$), and sickle cell disease (3.32 mg/dl, $p=0.0005$). Meta-analysis on severity of PH by the level of serum UA showed significantly higher mean pulmonary arterial pressure [5 studies, 574 subjects, 5.60 mmHg, $p=0.0006$] in the subjects with hyperuricemia than the subjects with normouricemia. Hazard ratio of death in PH was 1.17 for the subjects with hyperuricemia [7 studies, $p=0.02$]. Subgroup analyses of hazard ratio of death in PH by type of underlying diseases showed significantly higher hazard ratio of death in subjects with PH associated with interstitial lung disease [1 study, 2.90, $p=0.02$] and Eisenmenger syndrome [1 study, 1.61, $p<0.00001$]. However, the hazard ratio of death was not significantly higher in the subjects with PH associated with idiopathic pulmonary arterial hypertension. Meta-analysis also showed that the odds ratio of risk of PH when serum UA is 6.7mg/dl or more was 3.10 ($p=0.03$) and the risk ratio of PH when serum UA was 7 mg/dl or more was 8.50 ($p=0.05$).
Conclusions. Higher serum UA level was associated with both presence of PH and severe degree of PH. Hyperuricemia was also associated with higher hazard ratio of death in PH, especially in the subjects with interstitial lung disease and Eisenmenger syndrome, along with elevated risk ratio and odds ratio of PH. Therefore, serum UA seems to be one of prognostic factors of PH.

Key words: uric acid, pulmonary hypertension, systemic lupus erythematosus.

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ANALYSIS OF SLE PATIENTS HOSPITALIZATION IN A 10-YEAR PERIOD

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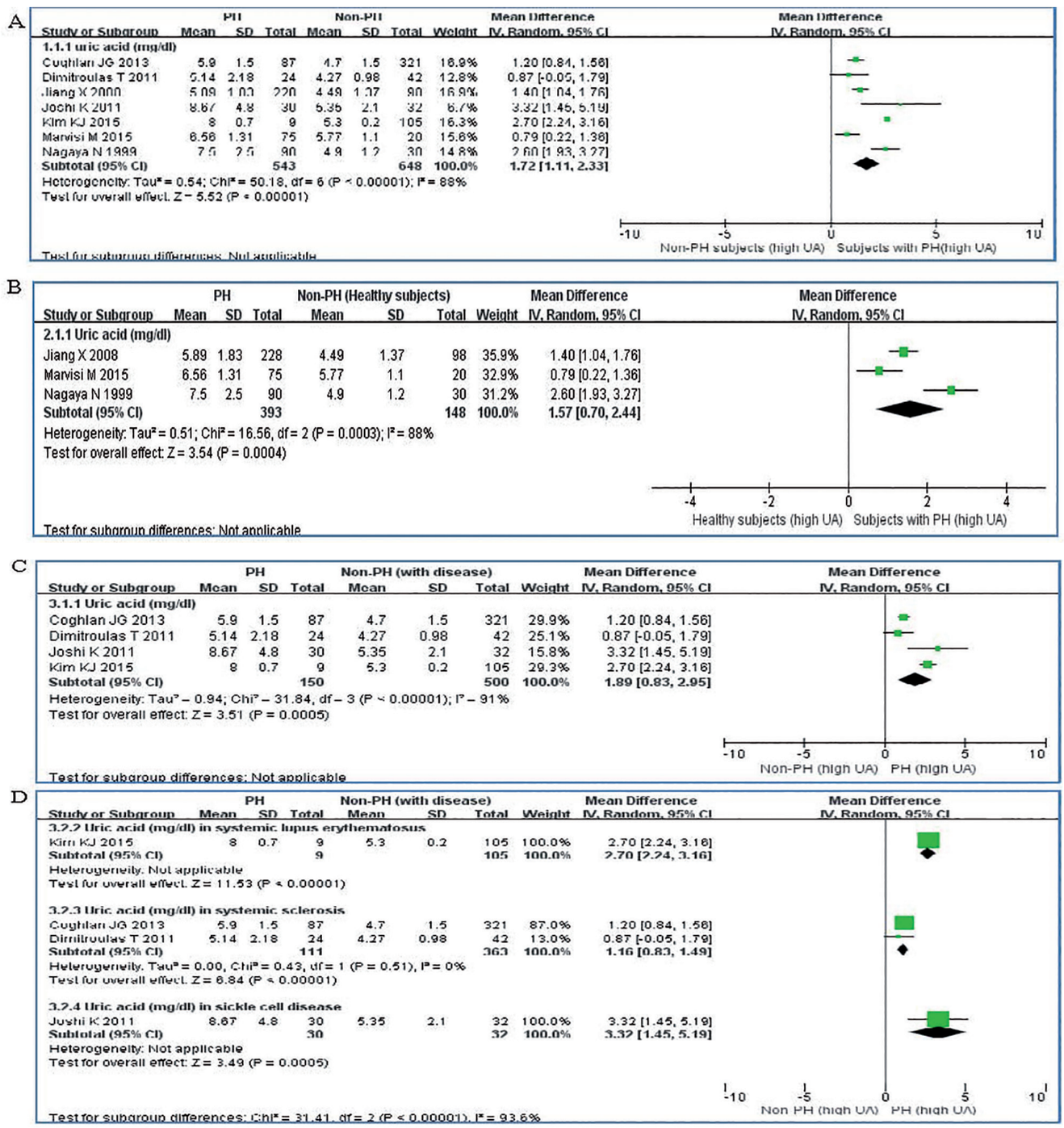
Objective. Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by a wide range of clinical manifestations and by a typically fluctuant course. Although SLE patients' survival has significantly increased in the last decades, morbidity and hospitalization are still considerably high. The aim of the present study was to analyze causes and outcome of SLE patients' hospitalization in a tertiary center over a 10-years period.
Design and Method. A retrospective analysis of all the admissions to the Rheumatology Unit in a 10 years period was conducted; hospital registries were used as a source of causes and time of hospitalization. The analysis was then focused on SLE patients (ACR criteria 1997): demographic, clinical and serological features were collected in a standardized computerized electronically filled form. In particular,

Figure. P8:180



frequency and causes of hospitalization, seasonality and mortality were evaluated. Disease activity was assessed by using SLE Disease Activity Index-2000 (SLEDAI-2K); chronic damage by using the SLICC Damage Index (SDI).

Results. In the included period between January 2003 and December 2013, 1615 patients have been admitted to the Rheumatology Unit: 315 (19.5%) were SLE patients (M/F 35/280; mean±SD age 38.5±12.3 years; mean±SD disease duration 135.2±99.7 months). The mean±SD time of hospital stay was 15.4±17.8 days. Disease flare was the most frequent cause of hospitalization, recorded in 66.7% of SLE patients, followed by infections (12.4%), active lupus nephritis admitted for renal biopsy (9.3%), infusional therapies (4.5%), drugs adverse events (1.4%), cancer (0.6%) and cardiovascular accident (0.3%), other (4.8%). The prevalence of disease flare was significantly higher than all the other causes of hospital admittance (p<0.000001). Mortality rate was 0.3%. Regarding seasonality (in the boreal hemisphere), most of SLE patients were admitted in the month of May (12.4%) without any significant differences among different seasons. The evaluation of disease activity was available for 194 patients and, at the time of admission, a median SLEDAI-2K value of 8 (IQR 5.5) and a median SDI value of 1 (IQR 1) were registered. As expected, SLE patients admitted for flare showed a significantly higher SLEDAI-2K value than those admitted for infections (p=0.02).

Conclusions. The retrospective analysis of all the hospitalizations in a Rheumatology Unit over a period of 10 years has highlighted that SLE patients' admissions are still frequent and that SLE flare is the most frequent cause of hospitalization. May was the most frequent month of hospital admission but no significant differences in seasonality were detected. Finally, a low incidence of death during the hospital stay was registered.

Key words: systemic lupus erythematosus, hospitalization, disease flare

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DISABILITY IN SLE PATIENTS WITH JOINT INVOLVEMENT: ASSOCIATION WITH ACTIVITY INDICES

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Objective. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting different organs and systems. The musculo-skeletal manifestations involve the majority of patients (incidence 69-95%), often representing the first feature at the onset of disease. It is characterized by different degrees of severity ranging from arthralgia to erosive/deforming arthritis. The presence of this involvement could determine a significant disability in daily activities, leading to a worsening in the quality of life. The primary endpoint of the present study was to evaluate the disability in a cohort of SLE patients with joint involvement by using the Health Assessment Questionnaire (HAQ). Secondly, we aimed at assessing the correlation between disability and disease activity indices.
Design and Method. We evaluated 88 patients (M/F 8/80, mean age ± SD 46.9±15.7 years, mean disease duration ± SD 150±121.44 months) affected by SLE (ACR 1997 revised criteria). According with the study protocol, only patients with at least one tender joint at the time of evaluation were enrolled and they were sub grouped according to the presence of arthralgia or arthritis. The HAQ was administered to all patients: disability was identified for all HAQ values higher than 0. The disease activity was assessed by SLEDAI-2K and ECLAM. Clinical evaluation included tender and swollen joint counts (0–28), patient's assessment of pain on visual analogue scale (VAS, 0-100) and global health assessment by the patient and the physician (GH, 0-100). These parameters have been used in order to assess DAS28, CDAI and SDAI.
Results. A condition of disability was identified in 81.8% of SLE patients, with mean ±SD HAQ value of 0.7±0.6. Fifty-four patients (61.4%) showed a HAQ value equal to or higher than 0.5. Disability was significantly more frequent in patients with arthritis than in those with arthralgia (97.4% versus 73.8%, p=0.000003). Moreover, the HAQ values were significantly higher in presence of arthritis compared with arthralgia (0.86±0.7 versus 0.46±0.42, p=0.02). A positive correlation between the HAQ values and DAS28 (R=0.48; p=0.0001), CDAI (R=0.3; p=0.01) and SDAI (R=0.43; p=0.003) was identified. Conversely, no correlations were registered between HAQ and global activity indices SLEDAI-2K (p=0.2) and ECLAM (p=0.6).
Conclusions. Our study demonstrated a high prevalence of disability in SLE patients with joint involvement, more frequent and severe in patients with arthritis compared with those with arthralgia. Notably, the HAQ, used to assess disability, showed a significant correlation with organ specific activity indices (DAS28, CDAI, SDAI) but any correlation with global indices (SLEDAI-2k, ECLAM). This result confirms the low sensitivity of these latter in the assessment of joint involvement and underlines the possible role of arthritis composite indices.

Key words: lupus, arthritis, HAQ

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SYSTEMIC LUPUS ERYTHEMATOSUS: A RETROSPECTIVE STUDY OF MUCOCUTANEOUS FEATURES IN SOUTH AFRICANS

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Objective. The aim of this study was to describe the prevalence and spectrum of mucocutaneous manifestations of Systemic Lupus Erythematosus in a largely black population at a tertiary hospital in South Africa.
Design and Method. In this retrospective study, clinical features, with special reference to mucocutaneous manifestations of SLE, were extracted from the case records of 298 patients attending the Lupus Clinic, Chris Hani Baragwanath Academic Hospital, Soweto. All patients met the SLICC classification criteria for SLE. Cutaneous lupus was classified into specific and non-specific cutaneous features. Specific cutaneous lupus subtypes included chronic cutaneous lupus, subacute cutaneous lupus (SCLE) and acute cutaneous lupus (ACLE). Bullous lupus erythematosus and Rowell's syndrome were classified independently. Chronic cutaneous lupus included discoid lupus erythematosus (DLE), chilblain lupus, lupus panniculitis. Non-specific cutaneous features included Raynaud's phenomenon, alopecia (both scarring and non-scarring), melanonychia, periungual telangiectasia, leukocytoclastic vasculitis, erythromelalgia, sicca, calcinosis cutis and oral or nasal ulceration.
Results. Most patients were black African females (255; 85.5%). The female to male ratio was 15: 1. The mean (SD) age at presentation and disease duration were 35 (13.5) and 7.95 (5.8) yrs, respectively.
The commonest presenting feature was arthritis/arthralgia in 188 (63%) patients. Cutaneous changes were the second commonest presentation affecting 166 (55.7%) patients. DLE was the presenting cutaneous disease in 149 (50%) patients whilst acute cutaneous lupus was the presenting symptom in 92 (33%) patients. Overall, 276 (92.6%) patients developed some form of cutaneous manifestation during the course of their illness. Non-specific cutaneous findings affected 263 (88.2%) patients while specific cutaneous disease affected 227 (76.1%) patients.

Table I. Specific and non-specific cutaneous findings.

Specific cutaneous disease	n	(%)
DLE	166	(55.8)
Generalised DLE	75	(25)
ACLE	92	(33)
SCLE	10	(0.3)
Bullous lupus erythematosus	5	(0.15)
Non-specific cutaneous signs		
Oral or nasal ulcers	129	(43.2)
Raynaud's phenomenon	125	(41.9)
Melanonychia	117	(39.2)
Sicca	46	(15.4)
Periungual telangectasia	36	(12)
Livedo reticularis	35	(11.7)
Alopecia /non-scarring)	18	(6)

Conclusions. In this predominantly Black African cohort of SLE patients, cutaneous disease was the second commonest presenting feature. There was a strikingly high frequency of DLE, particularly generalized type, occurring even more commonly than ACLE as the presenting feature of SLE.
Of the non-specific features, melanonychia was especially common, occurring in almost 40% of patients

Key words: SLE, cutaneous lupus erythematosus, South Africa

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LUPOSOMES - CIRCULATING EXTRACELLULAR VESICLES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. The sustained autoimmunity and the systemic type I interferon response in SLE may be due to clearance defects. It is not known if the disease is aggravated or triggered by abnormal amounts or types of subcellular materials, such as cell fragments and vesicles that are normally cleared by non-proinflammatory mechanisms. We therefore profiled the protein content of circulating EVs from SLE patients and controls using tandem mass spectrometry.
Design and Method. EVs were isolated from platelet-poor plasma from patients (SLE, n=45; Systemic sclerosis (SSc), n=38) and healthy controls (HC, n=50) by repeated 18,900xg centrifugations. Samples were proteolytically processed and the peptide fragments were analyzed by tandem mass spectrometry. Proteins were annotated and quantitated based on their intensity values and compared between the groups using non-parametrical statistics and correction for multiple comparisons.
Results. About 1100 individual proteins were identified in the SLE/HC (1139 proteins) and the SSc/HC (1032 proteins) cohorts. Data showed that the SLE-EV proteomes were distinctly different between SLE and SSc patients and between SLE and HC. The differences between EVs in the SLE and SSc and healthy control groups allowed an almost complete differentiation between these three groups. The data suggest a markedly increased production of abnormal EVs in SLE from parent cells characterized by profound metabolic, cytoskeletal, intracellular signaling, and mitochondrial alterations.
Conclusions. The primary pathology in SLE is an increased production of abnormal EVs that are released to the circulation and become immunogenic because of an increased amount and/or inflammatory capabilities. These EVs, that we hypothesize are specific for SLE and therefore call luposomes, cannot be appropriately handled by normal non-inflammatory clearance mechanisms. Our findings pave way for new candidate biomarkers, support particle clearance disturbances as a central disease mechanism, and give insight into new treatment options in SLE.

Key words: extracellular vesicles, proteomics, luposomes

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JACCOUD ARTHROPATHY: CLINCAL AND SEROLOGICAL CHARCTERISTICS

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Objective. To describe a series of patients with Systemic Lupus Erythematosus (SLE) complicated by Jaccoud Arthropathy (JA) and evaluated in our department during the last year.
Design and Method. All the patients with a documented history of articular involvement and a Jaccoud's Index score>5 were included in the study. Clinical features were defined according to the ACR 1997 classification criteria. Demographic, laboratory and clinical features (in particular cumulative ACR criteria, pharmacological treatments and articular characteristics) were retrospectively obtained by a medical records revision. SLE disease activity was assessed using SLEDAI-2K and ECLAM, articular disease activity using DAS-28 index.
Results. The study included 23 women with a mean age of 58.4±12.5 (34-81) years. The mean duration of SLE was 24.9±9.6 (7-38) years. A total of 17 comorbidities were observed: secondary Sjogren syndrome (9), fibromyalgia (3), secondary antiphospholipid syndrome (2), overlap myositis (2), thyroid disorder (1). Other clinical features, serological data, previous/concomitant treatments are shown in Table I.

		Anamnestic Data		Last Clinical Evaluation Data		
Cumulative ACR criteria 1997						
Malar rash		7 (30)		0		
Discoid rash		0		0		
Photosensitivity		13 (56)		3 (13)		
Oral ulcers		9 (39)		1 (4)		
Non erosive arthritis		23 (100)		5 (22)		
Serositis		6 (23)		0		
Renal disorder		9 (39)		0		
Neurological disorder		3 (13)		0		
Haematological disorder		12 (52)		2 (9)		
Immunological disorder		23 (100)		8 (35)		
Positive ANA		23 (100)		3 (2 negative, 18 not tested)		
Serological characteristics	Pos (%)	Neg (%)	Not Tested(%)	Pos (%)	Neg (%)	Not Tested(%)
Anti-DNA Ab	22 (96)	1 (4)	0	5 (22)	17 (74)	1 (4)
Anti-Sm Ab	5 (22)	18 (78)	0		-	
Anti-SSA Ab	11 (48)	12 (52)	0		-	
Anti-SSB Ab	5 (22)	18 (78)	0		-	
Anti-nRNP	5 (22)	18 (78)	0		-	
Anti-Cyclic-Citruil Pep. Ab	2 (9)	19 (82)	2 (9)		-	
Rheumatoid Factor	6 (26)	14 (61)	3 (13)		-	
Anti-cardiolipin Ab	9 (39)	14 (61)	0		-	
Anti-beta 2-blycoprotein I	10 (43)	13 (57)	0		-	
LAC	2 (9)	21 (91)	0		-	
Hypocomplementemia	20 (87)	-	0	5 (22)	-	0
Treatment						
Corticosteroids		23 (100)			22 (96)	
Hydroxychloroquine		22(96)			13 (57)	
Methotrexate		16 (70)			6 (26)	
Azathioprine		15 (65)			3 (13)	
Cyclosporine A		9 (39)			1 (4)	
Cyclophosphamide		6 (26)			0	
Mycophenolate mofetil		5 (22)			0	
Rituximab		3 (13)			2 (9)	
Belimumab		2 (9)			1 (4)	
Mepacrine		2 (9)			0	
Thalidomide		1 (4)			0	
Dapsone		1 (4)			0	
Leflunomide		0			3 (13)	
Disease Activity Indexes		(at onset)				
SLEDAI-2K median (IQ)*		8 (6-10)			2 (0-2)	
ECLAM median ± SD*		4 (2.6-4.5)			0 (0-1)	
DAS28 mean ± SD§		3.7±0.8			2.3±1.0	

*p<0.05 by the Mann-Whitney test.
§p<0.05 by the Student t test.

During the last clinical evaluation a severe active involvement was not observed in any patients; the median SLEDAI-2K and ECLAM scores were 2 (0-2) and 0 (0-1). Mean CRP and ERS values were 4.5±3.3 and 17.9±7.7. Only 5 (22%) patients had high levels of anti-DNA antibodies and 5 (22%) hypocomplementemia. The 96% of patients were receiving prednisone (weekly mean dose: 26.9±11.8 mg) associated with different DMARDs, principally hydroxychloroquine (57%), methotrexate (26%), azathioprine (13%) and leflunomide (13%). At the time of the study, only 5 patients had a DAS-28-score>2.6, in comparison with the high proportion of patients with active arthritis at SLE onset (91%). Ulnar drift (82%) and hallux valgus (71%) were the most often observed abnormalities. The 48% of patients had anti-SSA positive antibodies. Anti-beta-2-GP-I and anti-cardiolipin antibodies were positive in 43% and 39%, rheumatoid factor in 26%, anti- cytrullinated-peptide-antibodies (ACPA) in 9%.

Conclusions. in our study JA was associated with clinical detected arthritis, positive anti-DNA antibodies and hypocomplementemia at the onset of disease. Anti-SSA and atiphospholipid antibodies were quite frequently detected, while ACPA antibodies were rarely observed. Over time JA seems to predict a long-standing inactive form of SLE.

Key words: Jaccoud arthropathy, articular involvement, systemic lupus erythematosus.

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DIAGNOSIS, EVALUATION AND MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN CHINESE ADULTS: RECOMMENDATIONS FROM CHINESE SLE TREATMENT AND RESEARCH GROUP (CSTAR)

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Objective. Pulmonary arterial hypertension (PAH) is a rare but severe complication of SLE. Although other connective tissue diseases (CTDs) can also be causes of PAH, SLE is the most common underlying CTD of PAH in Asia, especially in China. Here, an evidence-based, expert-recommended clinical guideline towards SLE-associated PAH was developed.

Table Overarching principles and recommendations based on GRADE method

Overarching principles:	
1	Regarding to complexity the disease, the diagnosis, evaluation and management of SLE-associated PAH are recommended to be based on a multidisciplinary manner by specialists in rheumatology, cardiology, respiratory medicine, radiology, emergency medicine and rehabilitation medicine.
2	The management of SLE-associated PAH is recommended to be a shared decision between the patient, his/her family and his/her physicians.
3	The availability and financing of local medical resources should be considered in the management of SLE-associated PAH.
Recommendations:	
1	Early diagnosis and management are recommended in patients with SLE-associated PAH for a better outcome of survival.
2	SLE patients with pericarditis, pleuritis, positive anti-RNP autoantibody or Raynaud's phenomenon have higher risks to develop PAH. Annual transthoracic echocardiography and pulmonary function test are recommended in these patients for early detection of PAH.
3	Rheumatologists are recommended to be involved in consulting patients with the confirmed diagnosis of PAH for potential SLE or other underlying connective tissue diseases.
4	Right heart catheterization is recommended in confirming the diagnosis of PAH in patients with SLE. Other causes of pulmonary hypertension should also be considered in differential diagnosis.
5	A comprehensive disease evaluation, including pulmonary and cardiac function, serology, radiology, haemodynamics and quality of life, is recommended once the diagnosis of SLE-associated PAH is confirmed.
6	The treatment target of SLE-associated PAH should be a dual therapeutic goal towards both SLE and PAH, aiming at preventing clinical deterioration, ensuring long-term survival and optimizing health-related quality of life.
7	Immunosuppressive therapy against SLE is recommended in the treatment of SLE-associated PAH.
8	Primary therapy and target therapy of PAH is recommended in the treatment of SLE-associated PAH.
9	Patients with SLE-associated PAH are recommended to be involved in a clinical study of PAH with regular follow-up.
10	Regular evaluation and control of disease activity of SLE are recommended for a better outcome of SLE-associated PAH.

Design and Method. A national task force based on the Chinese Systemic Lupus Erythematosus Treatment and Research Group (CSTAR) and Chinese Rheumatism Data Center (CRDC) was gathered to investigate and formulate recommendations aiming at improving the diagnosis, evaluation and management regimens in China for patients with SLE-associated PAH. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method, based on systematic literature review was used to develop overarching principles and recommendations for SLE-associated PAH in Chinese adults.
Results. The task force investigated key areas regarding diagnosis, evaluation and management of SLE-associated PAH in Chinese adults by systematic literature review. Grading of recommendations and level of agreements were developed on two rounds of census-based panel meetings. Three overarching principles and ten recommendations achieving consensus from the panel meeting were identified. An extensive research agenda was also identified.

Conclusions. This is an evidence-based and expert-recommended clinical guideline towards SLE-associated PAH in Chinese adults developed by task force and panel meetings based on GARDE method. Follow-up research is needed to assess the quality of care and prognosis in patients with SLE-associated PAH receiving standardized, evidence-based care. Clinicians are also encouraged to focus on the research agenda to provide higher quality evidences in the management of disease in the future.

Key words: pulmonary hypertension, GRADE method, recommendations

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DO PATIENTS WITH SYSTEMIC LUPUS GET BETTER QUALITY OF CARE IN LUPUS CLINICS THAN IN GENERAL RHEUMATOLOGY CLINICS?

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Objective. Patients with SLE receive care from several physicians in varied health care settings worldwide. Herein, we compared the quality of care received by SLE patients at two settings within the same academic institution (lupus clinic or general rheumatology clinic) using validated SLE quality indicators (QI).
Design and Method. 100 consenting, consecutive patients fulfilling the ACR classification criteria for SLE who were receiving longitudinal care at Rush University Rheumatology outpatient clinic and at subspecialty Lupus clinic were recruited. A validated QI survey was updated, modified for self-report and administered during participants' routine SLE care visit. Retrospective rheumatology medical chart reviews were done in addition for complete evaluation of each QI performance. The overall performance rate and performance rates on 20 QIs were calculated for each of the two groups and compared using non-parametric tests. p-value <0.05 was considered significant.
Results. 60 patients from sub-specialty lupus clinic and 40 patients from general rheumatology clinic participated. Patients receiving care at lupus clinic had longer disease duration [10±6.6 vs 6.5±6.9 years; p=0.01] and met more number of ACR criteria [5.4±1.7 vs 4.7±1.0; p=0.01] compared to patients from general rheumatology clinics. The overall performance rate was significantly greater among lupus clinic as compared to rheumatology clinic SLE patients [87.5% (IQR: 16%) vs.71.1% (IQR: 19%), p=0.001]. Differences noted among the two groups were in counseling for use of sunscreen (98% vs 87%, p<0.036), testing for antiphospholipid antibodies within 6 months of diagnosis (70% vs 30%, p<0.001), recommendation for pneumococcal vaccine if on immunosuppressive medication/s (86% vs 50%, p<0.003), bone mineral density test performance if on chronic steroids (95% vs 48%, p<0.001) and prescribing a steroid sparing agent (100% vs 82%, p<0.007).
Conclusions. SLE patients seen in the dedicated lupus clinic had better overall and specific QI performance relative to general rheumatology clinics. This may suggest greater recognition among lupus clinic physicians of the importance of preventive care and disease monitoring among SLE patients. Of particular importance were the findings regarding vaccination and preventive use of sunscreen, as these may substantially affect morbidity in this patient population.

Key words: Quality indicators, Lupus clinic, General Rheumatology clinic

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Table Ia. Descriptives of study cohort.

Clinic	Lupus clinic	General Rheumatology Clinic	p-Value
Number of study patients (n)	60	40	
Age (mean ± SD) years	45.4±14.5	42.8±15.0	0.45
Gender:			
Female (n: %)	52;86.7	39;97.5	0.05
Ethnicity:			
African American (n; %)	20;33.9	26;65.0	0.02
Caucasian (n; %)	21;35.6	8:20.0	
Asian (n; %)	5;8.5	0;0	
Hispanic (n; %)	11;18.6	6;15.0	
Other (n; %)	2;3.4	0:0	
Education:			
Less than High School (n; %)	0;0	2;5.0	0.32
High School (n; %)	21;35.0	13;32.5	
College/University degree (n; %)	31;51.7	18;45.0	
Graduate degree/Higher (n; %)	8;13.3	7;17.5	
Insurance:			
HMO (n; %)	0;0	3;7.5	0.11
PPO (n; %)	27;45.0	10;25.0	
Medicaid (n; %)	11;18.3	7;17.5	
Medicare (n; %)	12;20.0	10;25.0	
Other (n; %)	9;15.0	9;22.5	
Charity care (n; %)	0;0	1;2.5	
No Coverage (n; %)	1;1.7	0;0	
Primary Care Physician:			
Yes (n; %)	56;93.3	37;92.5	1.00
Disease Duration (mean ± SD) years	10±6.6	6.5±6.9	0.01
Number of ACR criteria met:			
Malar Rash (n; %)	40;66.7	17;42.5	0.017
Discoid Rash (n; %)	13;21.7	5;12.5	0.30
Photosensitivity (n; %)	29;48.3	12;30.0	0.09
Oral ulcers (n; %)	28;46.7	13;32.5	0.21
Arthritis (n; %)	42;70.0	38;95.0	0.002
Serositis (n; %)21;35.0	12;30.0	0.67	
Renal disorder (n; %)17;28.3	7;17.5	0.24	
Neurological disorder (n; %)	8;13.3	1;2.5	0.08
Hematological disorder (n; %)	24;40.0	13;32.5	0.52
Immunologic disorder (n; %)	55;91.7	32;80.9	0.13
ANA (n; %)	56;93.3	39;97.5	0.64
PGA (median; IQR)	0.2;0.4 (n=58)	0.5;0.2-1.0 (n=3)	0.74
SLEDAI-SELENA (median; IQR)	2.0;4	2.0;4	0.53
SDI (median; IQR)	0.0;1	0.0;1	0.37
Medications:			
Steroids- ever (n; %)	49;81.7	31;77.5	0.62
Steroids- current (n; %)	20;33.3	18;45.0	0.29
Steroids Dose (median; IQR)	10;35	10;15	0.90
Hydroxychloroquine (n; %)	52;86.7	36;90.0	0.75
Methotrexate (n; %)	11;18.3	5;12.5	0.68
Axathioprine (n; %)	7;11.7	6;15.0	0.76
Mycophenolate mofetil (n; %)	16;26.7	6;15.0	0.22
Other medications* (n; %)	7;11.7	4;10.0	1.00

Table Ib. Performance on quality indicators (QI).

QI No.	Description of QI	Lupus clinic QI eligible (N)	Lupus clinic Met QI (n)	Lupus clinic PP (%)	General rheumatology Clinic QI eligible (N)	General rheumatology Clinic Met QI (n)	General rheumatology Clinic PP (%)	p-Value
1	ANA, CBC, Platelet, Creatinine, UA at diagnosis of 60 lupus	60	100	40	39	97.5	0.4	
2	AntidsDNA, C3/4, APL within 6 months of diagnosis	60	42	70.0	40	12	30.0	<0.001
3	Counselling for use of sunscreen	60	59	98.3	40	35	87.5	0.036
4	Influenza vaccine in last year if on ISM	37	36	97.3	24	20	83.3	0.07
5	Pneumococcal vaccine if on ISM	37	32	86.5	24	12	50.0	0.003
6	DEXA if have received ≥7.5 mg/day CS for ≥3 months	42	40	95.2	25	12	48.0	<0.001
7	Calcium and Vitamin D if have received ≥7.5 mg/d CS for ≥3 months or is post-menopausal	45	38	84.4	31	22	71.0	0.25
8	Antiresorptive agent if have received ≥7.5 mg/d CS for ≥1 month & central T-score ≤2.5 of h/o fragility fracture	10	10	100	3	3	100	N/A
9	Counselling about drugs at initiation	60	54	90.0	40	36	90.0	1.00
10	Baseline tests at initiation of drugs	59	58	98.3	40	38	95.0	0.56
11	Tests for drug monitoring	59	53	89.8	38	33	86.8	0.74
12	Steroid sparing agent if on ≥10 mg/day CS for ≥3 months	38	38	100	22	18	81.8	0.007
13	Follow-up tests (UA, CBC Creatinine done for LN at every 3 months	17	12	70.6	7	5	71.4	1.00
14	Treatment with ISM & CS within 1 month of diagnosis of Class 3/4 LN	13	13	100	7	7	100	N/A
15	Antihypertensive if have proteinuria ≥300 mg/d or GFR <60 ml/min & ≥2 BP readings >130/80	14	13	92.9	9	9	100	1.00
16	ACE inhibitor or ARB if have proteinuria ≥300 mg/d	15	14	93.3	7	4	57.1	0.07
17	Assessment of CVD risk & counselling	60	19	31.7	40	7	17.5	0.16
18	Tests in pregnancy (AntiSSA/SSB, APL)	9	6	66.7	5	2	40.0	0.58
19	Treatment of APS in future pregbancies	1	1	100	1	1	100	N/A
20	Reproductive health counselling	23	20	87.0	13	10	76.9	0.64

PP: Performance percentage; ANA: Antinuclear antibody; CBC: Complete Blood Count; UA: Urinalysis; APL: Antiphospholipid antibodies; ISM: Immunosuppressive medicationss; CS: Corticosteroids; HCQ: Hydroxychloroquine; MTX: Methotrexate; MMF: Mycophenolate mofetil; LN: Lupus Nephritis; ARB: Angiotensin receptor blocker; CVD: Cardiovascular Disease; APS: Antiphospholipid antibody syndrome.

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TEN-YEAR SURVIVAL AND ITS PREDICTORS IN A RETROSPECTIVE INCEPTION COHORT OF SLE PATIENTS FROM A CROATIAN TERTIARY CENTER

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Objective. Survival of European SLE patients has been assessed mostly in developed countries, where it has increased over decades. However, survival remains unexplored in Croatia and neighboring southeastern European countries. In this observational study we assessed survival in an inception cohort of SLE patients followed-up by the largest Croatian tertiary center.
Design and Method. We retrospectively assembled a cohort of SLE patients diagnosed between 2002 and 2011 (with at least 4 criteria of the American College of Rheumatology (ACR)), followed-up at our center until death or until the end of 2011. Deceased patients were identified by matching our patient database with the National Death Registry. For each patient we collected demographic data and data on fulfillment of ACR criteria. We estimated survival using Kaplan-Meier curves, with the year of diagnosis as the starting point. Features associated with lower survival in the univariate analysis were included in a multivariate Cox regression model to assess their independent role. The study was approved by the local ethics committee.
Results. Among 213 patients included in the study, 28 died and 14 were lost to follow-up. Mean follow-up time was 5.04±2.95 years. Five- and ten-year survival was 91.5% and 80.5%, respectively. Deceased patients were diagnosed at a later age compared to non-deceased patients (60±14 vs. 39±14 years). No difference between the two groups was observed in the proportion of females and the number of ACR criteria. Lower survival was observed in patients diagnosed after the age of 50 and patients with serositis, renal and neurologic disorder. Malar rash and photosensitivity were associated with higher survival. Following variables were included in the multivariate model: age at diagnosis, malar rash, photosensitivity, serositis, renal and neurologic disorder. Higher age at diagnosis, serositis, renal and neurologic disorder were associated with lower survival, while the protective role of skin features was not confirmed in the multivariate analysis.

Feature	*p*	HR	95% CI
Age at diagnosis (per year)	<0.001	1.10	1.06-1.13
Malar rash	0.388	0.67	0.27-1.68
Photosensitivity	0.661	1.25	0.46-3.46
Serositis	0.005	3.35	1.45-7.76
Renal disorder	0.023	2.46	1.13-5.37
Neurologic disorder	<0.001	8.73	2.68-28.42

HR: hazard ratio; CI: confidence interval.

Conclusions. Survival of our patients is lower than in similar European cohorts at the beginning of the millennium. This finding requires elucidation by assessing other factors known to influence SLE outcome. Serositis is considered a mild disease feature, so its role as a predictor of lower survival is unclear.

Key words: survival, inception cohort, tertiary center.

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ASSESSMENT OF WORKABILITY OF SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS. PRELIMINARY RESULTS FROM THE "RETURN TO WORK CLINIC" AT S. CAMILLO HOSPITAL IN ROME

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Objective. Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease characterized by clinical manifestations that may influence workability. The purpose of this study is to assess the impact of the disease on workability in a cohort of SLE patients.
Design and Method. 54 SLE patients (M/F=8/46; mean age 41.02±11.06 years, mean disease duration 13.37±9.27 years, mean age at disease onset 27.27±9.91), diagnosed according to 1997 ACR criteria, were consecutively enrolled. Patients underwent complete clinical assessment, including disease activity (ECLAM score) and patient disability in daily activities (HAQ). All patients filled out a questionnaire specifically designed for the assessment of work parameters. Patients were excluded when it was impossible to quantify the number of working hours (housewives, students, retired).
Results. According to the ISTAT CP2011 nomenclature, 19 patients were employees, 5 patients technics, 13 worked in trade and services, 2 high specialized workers, 5 artisans; 10 were in unskilled occupations. Mean ECLAM score at enrollment was 0.35±0.51. Mean hours to be worked per week amounted to 38 (full time) for 43 patients; to less than 38 hours (part time) for 9 patients; 2 patients didn't answer. Mean working days lost because of SLE was 71,72 ± 100,81 during the first year of disease from diagnosis; mean working days lost because of SLE was 13,86±17,70 during the year before enrollment. Mean HAQ score was 0,48±0,80 at enrollment; 16 patients had arthritis involvement; among them, 4 patients with arthritis presented the highest HAQ score (ranging from 1.6 to 2,87) with respect to those patients without arthritis (ranging from 0 to 1.37).
Conclusions. This study shows that SLE may influence workability and has a profound impact on the number of days lost at work.

Key words: workability, quality of life, disability.

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FACTORS WHICH DEFINE THE EARLIEST DISEASE SEVERITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND THE PATIENTS' RESPONSE TO THE PHARMACEUTICAL TREATMENT

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Objective. To study the factors defining the severity of SLE at the time of the diagnosis, as well as the ones influencing the response to the treatment.
Design and Method. 121 patients with Systemic Lupus Erythematosus were tested and treated while being observed by physicians of the rheumatology department of the hospital during a period of 5 years. The activity of the disease was determined in all patients according to the SLEDAI score both at the time of the diagnosis and after a median period of observation of 25, 9±23,2 months.
Results. The protocol that was applied included factors such as smoking habits, age, the detection of rheumatoid factor (RF) as well as the detection of anti-ds DNA antibodies. It was concluded that the SLEDAI score at the time of the diagnosis was defined by smoking and positive anti-ds DNA antibodies (positive correlation with both, $p<0.001$). As for the response to the treatment, the single factor analysis revealed that the SLEDAI score was lower in smokers, in patients positive to anti-ds DNA antibodies and the rheumatoid factor, as well as in patients who were older at the time of the diagnosis and were observed during a more extended time period and presented a higher SLEDAI score at the time of the diagnosis. However, the multiple factor analysis revealed that, in order of importance, only the earliest SLEDAI score and the duration of the observation-treatment were statistically significant. That is to say, the higher they were, the higher the decline of the SLEDAI score was ($p<0.0005$).
Conclusions. Smoking and the presence of anti-ds DNA antibodies in the patients' serum are two statistically significant factors that determine the disease severity. The response to the treatment is defined mainly by the earliest SLEDAI score and the duration of the treatment.

Key words: smoking, anti-dsDNA, RF

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VITAMIN D STATUS IN PHOTOTYPE VI SENEGALESE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): A CASE CONTROL STUDY

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Objective. Our aims were the following: to compare the rates of 25 hydroxyvitamin D levels in lupus patients and the controls, to identify variables associated with low levels of 25-OH-vitamin D.
Design and Method. we conducted a multicentric case-control study in three hospitals located in Dakar, the Senegalese capital. Thirty cases and 30 controls Data collection: Information regarding the medical history, clinical symptoms, and signs was registered at the time of serum sampling. Disease activity of SLE was evaluated according to the SLEDAI score. The 25(OH) D3 was determined by the test par electro chemiluminescence (ECLIA) for the *in vitro* determination of the total content of 25-hydroxyvitamin D (Elecsy® Vitamine D totale of Roche*). by age and sex were included.
Results. we report here the preliminary results about 25 cases and 25 controls. The mean age of our patients was 34.6 years [17-66 years]. The sex ratio was 0.19. Sixty percent of our patients had a low level of 25-hydroxy vitamin D (30 ng / ml with an average concentration of 25.24 ng / ml [10.23 to 45.14 ng / ml]. Less than half of the recruited subjects in both groups had sufficient vitamin D levels. Nevertheless SLE patients had significantly lower rates than controls (p=0,012). We found a significant association between the levels of 25-D Hydroxyvitamin and body surface exposed to solar radiation in both groups (OR =12,8 IC 95% [10,49-15,12] and p<10-4. Furthermore, we found a significant association between low vitamin D rates and various parameters including: age (OR =5,6 IC 95% [3,31-7,89]), duration of disease (9,3 [7,45-11,15] p=0.02), acute cutaneous involvement (OR=13,33 [11,0215,64] p=0.03), disease activity (OR=11 [9,07-12,93] p=0,027) and a hydroxychloroquine taken during a period exceeding 12 months (OR=22 IC 95%[19,53-24,47]). However, we found no association between dietary habits on the daily intake of calcium and phytates. Moreover, we found no association with skin damage, renal and haematological as well as immunological events or taking glucocorticoids and immunosuppressant and 25 OH vitamin D levels.
Conclusions. We found low levels of 25 OH vitamin D in phototype VI patients with SLE who living in sunny area in Dakar Senegal. Moreover we found significant association between low level and some clinical variables.

Key words: lupus, vitamin D, phenotype VI

P8:197

DIAGNOSTIC CRITERIA AND PATIENTS' OUTCOME: STUDY OF 82 ADULT PATIENTS IN AN INTERNAL MEDICINE UNIT

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Objective. The prescription of antinuclear antibodies (ANA) and antibodies to double stranded DNA (anti dsDNA) for patients either consulting in out patient unit or hospitalized via the emergency unit, for various reasons but all revealing criteria of autoimmunity evaluation, helps the clinician to establish the diagnosis of a significant number of cases of systemic lupus erythematosus (SLE) either isolated or associated with other autoimmune diseases. Our study aims to clarify the clinicoimmunolgical profile of SLE in adults, investigate the circumstances of discovery and the impact on the outcome.
Design and Method. This is a retrospective study of 8 years in an adult unit of internal medicine based on the confirmation of the presence of ANA by immune DOT test, anti ds DNA ± anti nucleosome antibodies. It concerns 82 patients (74 women and 8 men), the youngest was 21 and the oldest was 80. They all had a significant titer of ANA and anti dsDNA.
Results. Of 82 files, we find 1 case already diagnosed since the age of 11, 25 cases diagnosed after the age of 50. The revelation modes varied: 3 cases revealed by febrile cytopenia, 6 with thrombocytopenia, 2 with catastrophic antiphospholipid syndrome (CAPS), 4 with nephritis, 3 with cardiac manifestations (Libman Sachs endocarditis and pericarditis), 1 thrombotic microangiopathy (TMA), 4 with multiple autoimmunity diseases, 6 overlap syndrome, 1 case revealed by autoimmune neuropathy with anti MAG antibody, 1 declared by trigeminal neuralgia, 2 concomitant with dermatopolymyositis, 1 revealed by a masseter tumor and 1 necrotizing myopathy. The presence of circulating anticoagulant and or anti phospholipid antibodies was noted in 15 cases. The neurolupus (8) and the association with Sjögren syndrome (9) were common. 2 cases revealed after treatment by anti TNF alpha for rheumatoid arthritis and Cröhn's disease. The concomitant revelation with cancer was noted in 3 patients (2 solid and 1 Hodgkin lymphoma).
Lupus treatment in our study varied between antimalarial drugs for all of them, corticosteroids for many patients and other immunosuppressive drugs (azathioprine, cyclophosphamide and Mycophenolate mofetil). Treatment with anti platelets or anticoagulants prescribed in neurolupus and cases with circulating anticoagulant or anti phospholipid antibodies. 2 cases had plasma exchange (CAPS and TMA).
Fatal outcome happened in 3 cases (1CAPS, 1 cancer and 1 neurolupus).
Conclusions. Wandering before establishing a diagnosis of lupus is not rare, due to its heterogeneous clinicobiological manifestations as mode of revelation.
The presence of anti dsDNA and ANA still the major key of diagnosis. In our study the neurolupus consists the major entity with sometimes of poor outcome, on the other hand, the cases of renal affection didn't show aggravation due to the adopted aggressive strategy of treatment by immunosuppressive drugs.

Key words: lupus, diagnosis, outcome

P8:198

FACTORS INFLUENCING ON HEALTH-RELATED QUALITY OF LIFE IN KOREAN FEMALE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Health-related quality of life (HRQoL) among systemic lupus erythematosus (SLE) patients is reduced, because SLE can significantly impact both physiological and psychological functioning. With the advent of new treatment and better understanding of the disease, survival has improved in recent decades. However, this has not translated into improvement in HRQoL. To improve the HRQoL in SLE patients, it might be the clinically important and constructive theme to investigate that which is the most important factor among the fibomyalgia, depression, sleep quality, SLE activity and SLE duration.The objective of the present study is to evaluate the contributing factors for reduced HRQoL for reduced HRQoL in Korean female patients with SLE.
Design and Method. Subjects were selected from the five affiliated hospitals in South Korea. This study included 152 Korean female patients with SLE and 139 age, and sex-matched healthy controls. The HRQoL measurement was made using the SF-36 and Euroqol EQ-5D. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). We used the Patient Health Questionnaire 9 (PHQ-9) to identify depression. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale was used to measure fatigue. SLE clinical parameters, disease activity and cumulative damage, and steroid doses were evaluated. SLE disease activity was scored using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) by the attending physicians. Disease damage was scored using the Systemic Lupus International Collaborating Clinic/American College of Rheumatology Damage Index (SLICC/ACR-DI).
Results. The scores of HRQoL, including overall scores as well as the physical component summary (PCS) and mental component summary (MCS), were lower in Korean female patients with SLE, than in age-matched controls. Global PSQI was also higher in SLE patients than controls, indicating the poorer sleep quality in SLE patients. Over the 60 percent of SLE patients were defined as bad sleeper (PSQI>5), whereas it was found only in one-third of the control subjects. Fatigue was more severe in SLE patients, than control female subjects. The prevalence of clinically significant depressive symptoms (PHQ-9 >= 10) was 21.7% in SLE patients, whereas its was shown only in four among 139 control subjects (2.9%). In our study, fatigue severity, depressive mood and sleep quality of SLE patients were significantly correlated with EQ-5D indices, SF36 PCS and SF36 MCS scores. Logistic regression analysis revealed that low education level, high organ damage index, and poor sleep (PSQI>5) were independent risk factors for deteriorated HRQoL in Korean female patients with SLE.
Conclusions. The poorer quality of life in SLE patients can be improved by managing sleep quality.

Key words: sleep, depression, quality of life.

P8:199

CHILDHOOD LUPUS IN A REFERRAL MEDICAL CENTER: PREDOMINANCE OF CUTANEOUS MANIFESTATIONS

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Objective. The Children's Hospital at Dartmouth (CHAD) is the major referral center for pediatric care in northern New England with a catchment area that comprises about 1.6 million people. I reviewed all cases of pediatric lupus seen at this medical center between 1/1/2011 and 12/31/2015

Design and Method. Computerized search of clinic and hospital discharge diagnosis of systemic lupus erythematosus (ICD 9 710.0) for patients < or = 18 years old were obtained after Institutional Review Board expedited approval for this search was obtained. A total of 66 patients were identified and deidentified charts were reviewed, manifestations were noted and compiled. Descriptive statistics were calculated.

Results. see inserted image:

Table 1: Demographic data, presenting complaint and serologic features

Table 2: Type of skin manifestation, organ system involvement, and organ system associations.

Table 3: Treatment

Age at onset, age at diagnosis and time interval between onset and diagnosis is shown in Figure 1.

Table 1

Patient Characteristics		Presenting Complaint		Serology	
Female	57	Skin	34	ANA+	58
Male	9	Joint	20	ANA-	8
Caucasian	56	Chest pain	3	C' abn	23
African American	2	Other	9	C' nl	20
Asian	4			DNA ab +	17
unknown	4			DNA ab -	13
				APL +	12
				APL -	6

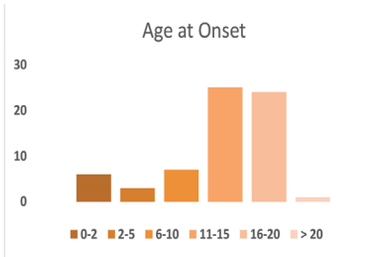
Table 2

Types of Skin Manifestations		Organ System Involvement	
Raynaud's	23	Musculoskeletal	29
Photosensitivity	16	Neurologic	16
Alopecia	13	Cardiac	8
Mucosal Ulcers	8	Pulmonary	5
Acute cutaneous	35	GI	1
Discoid	1	Renal	11
Neonatal	4	Hematologic	2
SCLE	2	Dermatologic	58
bruise/petechiae	4	**Associations**	
Chilblain/pernio	3	Renal +Skin	3
Hive	4	Renal + Skin + Jt	5
LCV	1	Renal - Skin - Jt	3
bullous	1		
calcinosis cutis	1		
no skin	8		

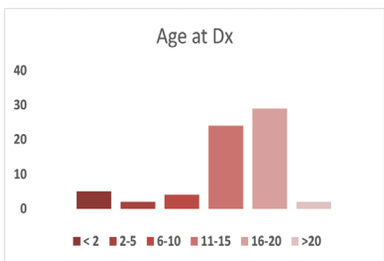
Table 3

Therapy	
Hydroxychloroquine	42
DMARD (MTX)	7
Biologic	8
IVIg	2
Cyclophosphamide	6
Mycophenolate	13
Azathioprine	5
Colchicine	3

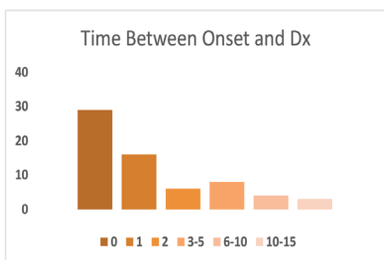
Age at Onset	
0-2	6
2-5	3
6-10	7
11-15	25
16-20	24
> 20	1



Age at Dx	
< 2	5
2-5	2
6-10	4
11-15	24
16-20	29
>20	2



Time Between Onset and Dx	
0	29
1	16
2	6
3-5	8
6-10	4
10-15	3



Conclusions. Unlike other series of pediatric age patients with SLE the majority of patients in this cohort presented with dermatologic manifestations and skin disease was present in over 80% of our patients. This may reflect the Caucasian predominance of our group or other clinical, referral and socio economic factors. However, this may more accurately reflect the clinical features of lupus in pediatric patients outside of major metropolitan areas.

Key words: pediatric, cutaneous, hydroxychloroquine

P8:200

CAN WE IDENTIFY WHO BENEFITS FROM MYCOPHENOLATE MOFETIL IN SYSTEMIC LUPUS ERYTHEMATOSUS? A SYSTEMATIC REVIEW

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Objective. The aim of this systematic review was to summarize the evidence examining factors measured at baseline and during treatment associated with a response to mycophenolate mofetil (MMF) in systemic lupus erythematosus (SLE).
Design and Method. Two reviewers independently assessed the methodological quality of the randomized clinical trials (RCT) using the Cochrane Collaboration risk of bias tool and cohort studies using the QUality In Prognosis Studies tool. The quality of subgroup analysis was also evaluated. The Grading of Recommendations Assessment, Development, and Evaluation working group approach summarized the quality of evidence (QoE), considering the risk of bias, imprecision, inconsistency, indirectness, and publication bias.
Results. Table I shows the main characteristics of prognostic studies. The quality of evidence for the prognostic value of age at study entry, gender and race was low, mainly due to exploratory or insufficient subgroup analysis, risk of bias and imprecision. The prognostic value of baseline laboratory parameters (glomerular filtration rate, proteinuria, serum creatinine) and changes during treatment (complement, proteinuria, anti-dsDNA) is very low due to post hoc subgroup analyses, risk of bias, indirectness and imprecision. One very-low QoE observational study showed that renal pathological classification (concomitant membranous lupus nephritis) may be an independent factor for no remission. However, this was not confirmed by subgroup analysis of RCT or observational cohorts. Drug-related factors (concomitant hydroxychloroquine therapy or MMF treatment less than 18 months) were associated with response and relapse, respectively; the MMF dose was not associated with adverse events (reduced IgG levels) in very-low to low QoE studies. One small cohort study found that a mycophenolic acid area under the curve more than 30 mg·h·L-1 was associated with renal response but not with side effects (infections).
Conclusions. In SLE patients, evidence for predictors of outcomes with MMF is limited. Our results should be treated with caution due to heterogeneity between studies, and the risks of bias identified. Future studies of predictors measured at baseline and during treatment should be designed using 'a priori' hypotheses and adequate statistical power.

Key words: systemic lupus erythematosus, mycophenolate mofetil, prognosis

Table (P8: 200)

Study ID	Setting	Design	No patient	Dose MMF	Follow-up	Predictor	Outcomes	Adjustment for confounders
Alexander 2014	India	PC	34	1.5 g/d at entry‡	12 m	MPA AUC MPA trough plasma concentrations	Renal response Adverse events	Not indicated
Cortes-Hernandez 2010	Spain	PC	70	1 g two times a day	24 m†	Age, improvement serum albumin levels, persistent anti-dsDNA, persistent hypocomplementaemia Histopathological class	Renal response Renal relapse Treatment failure	Not indicated
Kasitanon 2006¥	USA	RC	29	2120.7 mg/day†	12 m	Concomitant HQC use	Complete renal remission in MLM	Presence of anti-ds-DNA antibody
Kasitanon 2008¥	USA	RC	29	2000 mg/day (starting dose)	12 m	Mixed MLM	Complete renal remission	Not indicated
Laskari 2011	Greece	RC	44	2 (1.2-3) g/day‡	30 m‡	Duration of MMF	Relapse Side effects	No
Lu 2008	China	PC	213	MMF initiated at 1.0 g/day (<50 kg); 1.5 g/day: 50-70 kg and 2.0 g/day:: >70 kg	24w	Baseline serum creatinine Histopathological class	Renal remission	Not indicated
Nannini 2009	USA	RC	29	1328 mg/day†	14 m†	Concomitant HQC use	Disease flares	Not indicated
Rivera 2012£	Spain	RC	90	2,g/day‡	36 m‡	Gender, Poor renal function Histopathological class	Complete response Infectious	Age, gender eGFR, LN class and proteinuria
Rivera 2013£	Spain	RC	56	1 g/day‡	24 m (3-108)‡	Gender, Proteinuria Poor renal function	End-stage disease Mortality	Gender, baseline eGFR, proteinuria and LN class
Tselios 2016	Canada	RC	177	Non renal group: 1350 mg/day† Renal group: 1687.5 mg/day†	12 m	Renal involvement	Extrarenal manifestation improvement	Not indicated
Yap 2014*	China	RC	46	1.8±0.3 g/day at six m and 1.2±0.4 g/day at 12 m†	12 m	Proteinuria, serum creatinine, anti-dsDNA and C3, white cell count lymphocyte count at 6 m MMF dose/body weight	Circulating IgG level	Proteinuria, serum creatinine, anti-dsDNA, C3, white cell count and lymphocyte count at 6 m; MMf dose/body weight

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ILLNESS NARRATIVES AMONG SLE PATIENTS. AN ANTHROPOLOGICAL PERSPECTIVE OF LIVING WITH CHRONIC DISEASE

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Objective. The current research aims at providing a representation of SLE patients' lived experience by collecting their illness narratives, trying to describe a wider frame in which people's individual experience is linked to their sociocultural context, besides the restricted biological side of the disease.
Design and Method. The research, carried out over 5 months, was organized according to an anthropological investigation method based on a qualitative analysis of the collected data: participant observation during the events organized by Gruppo LES Italy in Rome and recorded semi-structured interviews with a sample of 11 patients (10 women and 1 man, aged 23 to 60 years).
Results. The stories I collected were mostly centered on the illness event, especially on how it has been affecting the person's life, from the diagnosis to what being ill means today. Moreover, not ignoring the proper scientific aspect of the disease -that is the autoimmunity caused by SLE leads to the production of antibodies which attack the organism itself provoking the destruction of the self- the research shows how the patients, starting from their medical condition, undertake a process of resignification of their whole existence, not only the illness event. The patient, then, simultaneously acts on two levels: on one side, he/she is an ill body who needs to have his/her normal physiological function restored, so he/she tries to recover his/her natural and biological balance; on the other side he/she redefines the ontological structures by which the individual perceives and acts in the world. By reporting some examples from illness narratives it is possible to notice the importance patients give to the role of the doctor: for them, he/she should be able to understand and pay attention not only to the pathological situation - seen as blood count and medical examination - but also to the way the patient interprets that situation. Perhaps the most impressive aspect is how some patients, referring to a "positive" mental ability, succeed in dealing with the illness, 86way the pain according to a method which is totally alien to the biomedical concept of disease.
Conclusions. A strong connection between mind and body emerges in all the collected stories: seen as complementary, they both contribute to the definition and the construction of the new world where the patients finds themselves living in. Therefore what patients ask for is a greater attention for the psychological aspect on the part of physicians, who should not limit themselves to the biological analysis of the disease. This research could help with cooperation between physicians and patients: presenting these illness narratives might generate a dialogue in which a different point of view on what it means to live with a chronic disease comes to light, instead of it being seen simply as an organic disfunction.

Key words: sociocultural context, mind-body, doctor-patient relationship

Poster session 9: Challenges in management of SLE (2)

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CAPABILITIES OF EUROPEAN LUPUS GROUPS; MEMBERS OF LUPUS EUROPE

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Objective. To identify the different structures and capabilities among European lupus groups.
Background. Lupus groups will have a significant role to play in healthcare. LUPUS EUROPE is an umbrella organization of 24 national lupus groups in Europe.
Design and Method. An online survey was distributed to validated contacts within member groups. It had four sections: (i) group aims, structure and funding (ii) resources and network (iii) the situation for people living with lupus in the country (iv) the lupus group needs and wishes in capability building nationally and on European level. Questions offered single answer, multiple response or commentary.
Results. 14 groups (58%) responded from Belgium (2), Cyprus, Denmark, Finland, Greece, Italy, Iceland, Netherlands, Norway, Spain, UK, Sweden and Switzerland. Key results included:
- 13/14 groups have an elected board of volunteers, 11/14 are run by volunteers;
- 9 of the 14 groups are affiliated with the arthritis and/or rheumatism associations in the country;
- 12/14 groups cited membership subscriptions as the main source of funding;
- 8/12 groups identified need for capacity building in political lobby activities.

More than 2/3rds of the groups expect LUPUS EUROPE to support member groups in their advocacy work and provide scene and opportunity to have more people educated and engaged in improving lupus patient interests in research and political work.
Conclusions. There is a diverse range of capabilities and needs amongst national European lupus groups; some are very well established with significant capabilities, while others need capacity building in priority areas.

Key words: advocacy, patient organizations, patient partner in research.

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OUTCOME OF FILIPINO CHILDREN WITH LUPUS NEPHRITIS TREATED WITH A MODIFIED TREATMENT REGIMEN USING CYCLOPHOSPHAMIDE

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Objective. The current therapeutic strategy for childhood-onset lupus nephritis (LN) involves an induction phase which aims to promote remission, and a maintenance phase to prevent relapses and control disease. Various regimens have been used by different centers worldwide, which may differ in the drug of choice and dosage, as well as in the duration of the induction and maintenance phases, because therapeutic response and report of adverse events vary according to the protocol used and in patient demographics. Although the outcome of lupus nephritis has remarkably improved, a significant proportion still do not attain remission despite various modifications in dose and frequency of the pulses. Achieving the goal of treatment of disease control and maintenance of remission should be hand-in-hand with very minimal side effects, if none is not possible. This study evaluated treatment outcome and adverse event occurrence in Filipinos with childhood-onset LN who received 9 monthly and 5 quarterly cyclophosphamide pulses.
Design and Method. A chart review was done on patients seen from year 2006 to 2014 at the University of Santo Tomas Hospital who completed the modified regimen.
Results. A total of 19 patients completed the modified cyclophosphamide pulse therapy (94.7% female, mean age 11.2+3.7 years at lupus diagnosis, mean nephritis duration upon completion of treatment 30.6+5.2 months), with a minimum follow up duration of one year. At 9 months of treatment, 47.4% (9/19) already reached complete remission, and 52.6% (10/19) were in partial remission. Upon completion of 9 monthly and 5 quarterly pulses, 94.7% (18/19) was with complete treatment response. One patient (5.3%) relapsed during the maintenance phase and was in partial remission at the end of the treatment. The random urine protein:creatinine ratio and disease activity were significantly improved in all 19 patients. Treatment failure was not noted in any of the patients at the end of 9 months and at the completion of treatment. Reported adverse events were gastrointestinal symptoms (100%), mild infections (94.7%), alopecia (89.5%), severe infections (10.5%), menstrual irregularities (33.3%), and hematologic disturbances (26.3%). All of the 19 patients are in remission during their most recent follow up. With the above data, we find that extension of the induction therapy by three months using standard dosing while maintaining the total cumulative dose by shortening the maintenance phase resulted in a favorable short-term outcome and adverse event occurrence, which is comparable to outcomes of other Asian cohorts.
Conclusions. A modified regimen of 9 monthly and 5 quarterly cyclophosphamide pulses may be an effective therapeutic option for childhood-onset LN.

Key words: cyclophosphamide, childhood-onset, lupus.

P9:204

HEALTH-RELATED QUALITY OF LIFE (HRQOL), THE EMOTIONALITY AND THE DAY-TO-DAY PROBLEM SOLVING AND COPING IN LUPUS PATIENT

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Objective. This document presents the results of a study performed to assess the Health-related Quality of Life (HRQOL), the emotionality and the day-to-day problem Solving and coping in lupus patients, compared to a control sample.
This research is intended to analyze how symptoms affect to patients and what is the level of impairment associated to the disease perceived by them.
Design and Method. The assessment was carried out by examining 35 lupus-diagnosed patients living in Madrid and an equivalent healthy sample control.
Three questionnaires were used for both samples: SF-36 for measuring HRQOL, PANAS for quantifying positive and negative affect, ISAP for analyzing problem solving and coping; additionally, a structured interview (LUPAM), built ad-hoc for this study in a Google Form, was filled exclusively by the lupus sample and included questions to evaluate pain level and perceived level of impairment.
Results. Main results found were that HRQOL level in lupus patients is lower than the average population, finding out differences also in the "past week Negative Affect" dimension.
Nevertheless, there were not found statistically significant discrepancies between patient and control samples regarding to Problem Solving and Coping.
Conclusions. The study proves that patients perceive lupus and lupus-related disability in a worse manner depending on the disease phase, while there are some possible solutions to improve this perception such as developing chronical pain programs.
Additionally, it can be concluded that deeper research in this field is needed (with wider samples and through different locations).

Key words: systemic lupus erythematosus, health-related quality of life, pain

P9:205

A RARE LUNG MANIFESTATION IN SYSTEMIC LUPUS ERYTHEMATOSUS: THE SHRINKING LUNG SYNDROME. A CASE REPORT AND REVIEW OF THE MOST RECENT LITERATURE

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Objective. Shrinking lung syndrome (SLS) is a restrictive lung disease due to impairment of respiratory muscles, rarely described in systemic lupus erythematosus (SLE).
Design and Method. Starting from a SLS case followed in our department, we searched all SLE SLS cases reported in literature from 2000 until April 2016, focusing on clinical features at presentation, instrumental and serological findings, as well as treatment strategy and outcomes.
Results. 34 years old female with ten years history of SLE with previous systemic and renal involvement and treated with low dose steroids, was admitted in our department for intermittent fever, worsening dyspnoea, orthopnoea and intermittent pleuritic chest pain in the last 9 months. The blood exams demonstrated

mild leucopenia, severe lymphopenia, anemia, ANA antibodies 1:640 with Ro/SSa and La/SSb specificity, presence of anti-dsDNA, low C3 and C4 levels and increased liver enzymes, without evidence of myositis. Pulmonary CT-scan excluded parenchymal or vascular disease, while pulmonary functional tests (PFT) were specific for extra parenchymal restrictive pattern. The diaphragm ultrasonography (US) revealed a reduced diaphragmatic motion with negative sniff test, so the patient was diagnosed with SLS complicating an active SLE and began treatment with high dosage steroids and, for high disease activity, mycophenolate and belimumab that are currently ongoing.
Overall, we identified 60 SLE SLS (59 cases from literature search and our current one), most of them adult (93% mean age 34±14 years) female (91%) with long standing disease (disease duration 80±14 months). The most frequent presentation symptoms were dispnoea (97.8%) usually without severe hypoxia and pleuritic chest pain (63.8%). Dry cough and fever were reported only in a minority of patients. Immunological findings showed an high frequency of positive ANA (100%), Ro/SSA (86%) and anti ds-DNA (73%).
Radiological exams (Chest X-ray and CT-scan), frequently, demonstrated only elevation of hemi-diaphragms or pulmonary atelectasis. Instead, PFT showed decreased pulmonary volumes with normal or only slightly decreased DLCO corrected for alveolar volume and severely reduced respiratory muscles strength tests.
Most of the patients were treated with a combination of increased steroids dosage and immunosuppressant, such us Cyclophosphamide (48%); Azathioprine (24%) and Mycophenolate (12%). In 4 patients was reported the successful use of Rituximab as second line therapy. Outcome data showed a PFT improvement in 80% of cases but a complete restoration was observed in only 4 patients.
Conclusions. SLS is a rare SLE manifestation with unclear pathogenesis and presents usually with worsening dyspnoea, pleuritic chest pain and characteristic PFT alterations without radiological significant abnormalities. Only few articles reported the use of diaphragm US in the diagnostic flow chart of SLS, so, its effective value has to be confirmed. This is the first report of a SLE SLS patient with signs of active disease treated with belimumab in association of mycophenolate.

Key words: shrinking lung syndrome, systemic lupus erythematosus, case report and review

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MULTIPLE AUTOIMMUNE SYNDROME: EXPERIENCE OF AN INTERNAL MEDICINE UNIT

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Objective. The multiple autoimmunity syndrome (MAS) is rare and is presented by the combination of at least 3 autoimmune diseases.
We searched the clinical and laboratory characteristics of patients with MAS among a group of 232 patients followed in our internal medicine unit for a connective tissue disease (systemic lupus erythematosus SLE, rheumatoid arthritis, Sjögren's syndrome SS, scleroderma, dermatopolymyositis) from 2008 to 2015.
Design and Method. This is a retrospective study based on the analysis of files of 14 patients with MAS.
The patients were all women, with mean age of 46.85 years (29-79 years).
There were no familial history conferring susceptibility for autoimmunity.
Results. The most frequent coexistent diseases found, were SLE (78.57%), SS (35.71%), scleroderma (35.71%), dermatopolymyositis (28.57%), primary biliary cirrhosis (14.28%), sclerosing cholangitis (14.28%), autoimmune atrophic gastritis (14.28%), inflammatory bowel diseases (14.28%).
Female gender, SLE, secondary Sjögren's syndrome, high titers of fluorescent antinuclear antibodies (FANAs), anti- DNA, anti-SS-A/SS-B antibodies were risk factors for MAS.
We noted the presence of antiphospholipid antibodies in 28.57% of cases.
One patient had developed sarcoidosis and another one had a concomitant Hodgkin lymphoma.
Conclusions. Our data is concordant with the data reported by the literature suggesting that gender and age of onset are interrelated factors influencing autoimmunity. MAS is frequent in SLE and secondary SS and it is influenced by clinical and immunological features.

Key words: multiple autoimmune syndrome, systemic lupus erythematosus, secondary Sjögren's syndrome

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DEPRESSION IN SAUDI PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A MULTICENTER STUDY

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Objective. Neuropsychiatric disorders including depression are common clinical manifestations of Systemic Lupus Erythematosus (SLE). Depression in SLE patients is under-recognized although it is a treatable clinical feature. This study is to determine the prevalence of depression and the relationship between depression and SLE disease characteristics.
Design and Method. This study is a multi-center cross-sectional study conducted in Rheumatology Clinics to determine the prevalence of depression and the relationship between depression and SLE disease characteristics in terms of age, gender, disease duration and severity, and steroid treatment in Saudi patients with SLE. The validated Arabic Beck Depression Inventory (BDI) questionnaire used to estimate the prevalence of depression. Data were analyzed via SPSS 17th edition software. Chi-square test or Fishers exact test, whichever is appropriate, was used for comparison of categorical variables. A two tailed p-value of <0.05 is considered as significant.

Sex			0.590
Male	2 (50)	2 (50)	
Female	20 (31.3)	44 (68.8)	
Marital status			0.728
Single	12 (36.4)	21 (63.6)	
Married	10 (30.3)	23 (69.7)	
Divorced	0 (0)	2 (100)	
Education			0.855
Elementary	2 (33.3)	4 (66.7)	
Secondary	9 (27.3)	24 (72.7)	
Bachelor	10 (38.5)	16 (61.5)	
No Education	1 (33.1)	2 (66.7)	
Income			0.403
Low	1 (25)	3 (75	
Intermediate	11 (26.8))	30 (73.2)	
High	10 (43.5)	13 (56.5)	
Employee status			1.000
No	19 (33.3)	38 (66.7)	
Yes	3 (27.3)	8 (72.7)	
Suicidal idea			1.000
No	22 (32.8)	45 (67.2)	
Yes	0 (0)	1 (100)	
Disease exacerbation			0.241
No	17 (37.0)	29 (63.0)	
Yes	5 (22.7)	17 (77.3)	
Disease Duration			1.00
≤6 months	1 (33.3)	2 (66.6)	
≥6 months	21 (32.3)	44 (67.7)	
SLEDI Score			0.661
No activity (0)	4 (36.4)	7 (63.6)	
Mild activity (1-5)	7 (28.0)	18 (72)	
Moderate activity (6-10)	9 (42.9)	12 (57.1)	
High activity (11-20)	2 (25.0)	6 (75.0)	
Very high (>–20)	0 (0)	3 (100)	
Steroid use			0.046
No	7 (58.3)	5 (41.7)	
Yes	15 (26.8)	41 (73.2)	
Immunosuppressive therapy			0.297
No	9 (40.9)	13 (59.1)	
Yes	13 (28.3)	33 (71.7)	
Antidepressant			0.096
No	19 (29.7)	45 (70.3)	
Yes	3 (75.0)	1 (25.0)	
Co morbidities			0.369
No	15 (29.4)	36 (70.6)	
Yes	7 (41.2)	10 (58.8)	
aPL			0.284
Negative	14 (28.6)	35 (71.4)	
Positive	8 (42.1)	11 (57.9)	
APS			0.738
No	18 (3.6)	39 (68.4)	
Yes	4 (36.4)	7 (63.6)	

All value are presented as n (%),

Results. A total of 68 SLE patients (64 women, 4 men with a median age of 30 years and median disease duration of 5 years) were included. Forty-six patients (67.6%) achieved scores indicating depression, of whom 33.8%, 20.6%, and 13.2% had mild, moderate and severe depressions respectively. Only one patient (1.5%) had a suicidal idea but no patient had a suicide attempt. 22 patients (33.2%) had a recent disease exacerbation within a year. 84% of patients had active SLE (36.8% had a mild activity, 30.9% had moderate, 11.8% had high activity scores, and 4.4% had very high activity scores). Fifty-six patients (82.4%) had received corticosteroid therapy with a median duration of steroid of 48 months and a median dose of steroid of 5 mg. Forty-six (67.6%) patients had received immunosuppressive therapies. Surprisingly, only four patients were treated with antidepressants.
In comparison between the two groups, there was a significant difference by using corticosteroid therapy (p=0.046) and depression. However, there was no association between disease activities (p=0.661) or disease duration (p=1.00) and depression. Indeed, neither positive aPL (p=0.284) nor APS (p=0.738) was associated with depression.
Conclusions. Our study revealed high prevalence of depression in Saudi SLE patients and most of our patients were not adequately treated, suggesting inadequate recognition and treatment of depression in SLE.

Key words: systemic lupus erythematosus, depression, Saudi

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SIX CASES OF MACROPHAGE ACTIVATION SYNDROME AS PRESENTING MANIFESTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Macrophage Activation Syndrome (MAS) is a life-threatening syndrome characterized by excessive immune activation. It can be triggered by conditions affecting immune homeostasis, such as infections, malignancies and rheumatologic disorders, including Systemic Lupus Erythematosus (SLE). In previous studies, prevalence of MAS among SLE patients ranged from 0.9% to 4.6%. The aim of our study was to describe the presentation and treatment of both MAS and SLE in patients with both syndromes.

Table I. Main clinical and laboratory features at diagnosis of SLE and MAS.

Clinical features of MAS n (%)		SLE ACR classification criteria	
Fever	6 (100%)	§Malar rash/Oral	5 (83%)
Hemorrhages	1 (17%)	ulcers/Photosensitivity/	
CNS dusfunction	0 (0%)	LED	
Lymphadenophaty	6 (100%)		
Hepatomegaly	4 (67%)	Arthritis	2 (33%)
Splenomegaly	4 (67%)	Nephritis	0
		Serositis	3 (50%)
		CNS disease	1 (17%)
		Haematological involvement	6 (100%)
MAS Laboratory Parameters median (IQR)		Autoantibodies n (%)	
WBC (x10^3/uL)	2.1 (1.8-2.3)	ANA	6 (100%)
Neutrophils (x10^3(uL)	1.5 (0.87-1.8)	anti-ds DNA	5 (83%)
HGB (g/dL)	7.6 (7-8.2)	anti-RNP	2 (33%)
PLT (x10^3/uL)	134 (72-142)	anti-Ro	1 (17%)
AST (U/L)	250 (166-402)	anti-Sm	1 (17%)
ALT (U/L)	111 (92-135)	antiphospholipid	3 (50%)
LHD (U/L)	769 (535-915)	Ab/LA	
Ferritin (µg/L)	4607 (1897-31533)	*Direct Coombs Test +	5 (100%)
Fibrinogen (mg/dL)	97 (35-170)	C3 mg/dl (n.v 80-160)	34 (28-70)
Triglycerides (mg/dl)	511 (317-605)	C4 mg/dl (n.v 10-40)	13 (7-17)
ESR (mm)	17.5 (9-24)		
CRP (mg/dl)	37 (10-49)		

*this test was available only for 5 patients. §at least one of these criteria: malar rash; Oral ulcers; Phosensitivity; LED: Discoid Lupus Erythematosus.
CNS: central nervous system; WBC: white blood cells; HGB: hemoglobin; PLT: platelet; AST: aspartate aminotrasferase; ALT: alanine aminotrasferase; LDH: lactate dehydrogenase; ESR: erythocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibodies; anti-ds DNA: anti double stranded DNA antibodies; anti-RNP: anti-ribonucleoprotein antibodies; LA: Lupus anticoagulant; n.v.: normal values.

Design and Method. Monocentric retrospective evaluation: patients with MAS according to HLH classification criteria were identified in our cohort of SLE patients (classified according to ACR and SLICC criteria) followed for at least 1 year between 1972 and 2014.
Results. Among 511 patients with SLE (mean age at diagnosis: 31 years +2), 6 patients (1.2%) with MAS were identified (all female). Their main clinical and laboratory features are reported in Table I. Median HLH score was 226.5 (IQR 204-254), with a probability of having MAS of 96%. In all cases MAS happened simultaneously to the onset of SLE. Median age at diagnosis was 31.5 years, median SLEDAI was 12. All patients had fever above 38°C, lymphadenopathy, hematological involvement, and high titer ANA positivity. Workup for infections and malignancies was negative in all cases. All patients were treated with corticosteroids (100%received intravenous immunoglobulin pulse of methylprednisolone); concomitant medications were: cyclosporin A in 83%, IVIG in 67%, granulocyte colony-stimulating factor in17%, mycophenolate mofetil in17%, etoposide in 17% and plasma exchange in 17%. Two patients required haemotransfusion.
All cases required hospital admission, and 2 were admitted in intensive care unit. No death from MAS was observed (median follow up: 34.5 months; IQR 25-48). One patient died 44 months after after MAS for pulmonary adenocarcinoma.
Conclusions. MAS is a rare complication in our SLE cohort and can complicate the onset of SLE, but it seems to be a very uncommon manifestation during the course of the disease.
Fever may be a red flag for possible MAS, particularly if temperature is persistently above 38° in absence of signs and symptoms of underlying infection.
In our series, all cases were treated successfully with immunosuppressive drugs and cytotoxic agents such as etoposide were used only in one case.

Key words: macrophage activation syndrome, systemic lupus erythematosus

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CLINICAL CHARACTERISTICS OF PATIENTS WITH SYSTEMIC LUPUS ERYTHROMATOSUS IN NAIROBI, KENYA

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Objective. Systemic lupus erythematosus (SLE), a chronic multisystem autoimmune disease with a wide spectrum of manifestations, shows considerable variation across the globe, although there is although data from Africa is limited. Quantifying the burden and description of symptoms of SLE across Africa can clarify the role of genetic, environmental and other causative factors in the natural history of the disease, and to understand its clinical and societal consequences.
Aim: To determine the clinical profile of systemic lupus erythematosus (SLE) patients at a tertiary care centre in Nairobi, Kenya.
Design and Method. Patients fulfilling the 2012 SLICC criteria for SLE seen between January 2012 and January 2013 were included in the study.
Results. Hundred patients were evaluated for SLE over a one-year period. 97% of the study participants were female with a mean age of 36.6 years. 33 years was the mean age of diagnosis. The mean time duration of disease was 3years with a range of 0-13years. Non-erosive arthritis and cutaneous disease were the commonest initial manifestation. The patients had varied cutaneous, haematological, pulmonary, cardiac, renal and neuropsychiatric manifestations. Antinuclear antibody (ANA) assay and anti-dsDNA was positive in 82% and 52%. Patients on steroids, non-steroidal drugs and synthetic disease modifying anti-rheumatic drugs were 84%, 49% and 43% respectively. None of the patients were on biologic disease modifying anti-rheumatic drugs.
Conclusions. SLE is a multisystem disorder affecting predominantly young females. Polyarthritis and cutaneous disease were the most common clinical feature. This is comparable to other studies done in black African population. We found a higher prevalence of haematological and lower rate of renal disease as compared to other studies done in black Africans. The Antinuclear antibody (ANA) assay and anti-dsDNA was positivity was lower than those in other studies on black Africans. Majority of the patients are on steroids.

Key words: SLE, Nairobi, Kenya

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A STUDY AND RECORD OF THE EARLY SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN A HOSPITAL IN NORTHWESTERN GREECE

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Objective. To analyze the prevalence and the typical clinical manifestations of SEL in 173 patients.
Design and Method. The average age of the patients during the outset of the disease was 31 years of age while the one when primarily diagnosed with the disease was 33 years of age. The proportion of female and male patients was 6.5:1.The most common early symptoms of the disease were arthralgias, rash, arthritis and fever while the incidence of manifestations that are not considered diagnostic as far as SEL is concerned such as Raynaud syndrome and lymphadenopathy, was particularly high.
Results. There were many dissimilarities in the manifestations of the disease in accordance with the age and gender of the patients. Fever, rash, and Raynaud syndrome were statistically prevalent in patients with a disease outset earlier than 14 years of age while symptoms such as sicca syndrome and gastrointestinal symptoms were more prevalent in patients with a disease outset later than 50 years of age. Similarly, female patients manifested arthralgias as an early symptom of the disease more often in comparison to the male patients to whom a particularly high rate of episodes of renal vascular thrombosis and strokes was noticed.
Conclusions. The key question that emerges is whether patients with different types of clinical manifestations of Lupus also show variations in the prognosis of the disease.

Key words: age, clinical manifestations, prognosis

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CHRONIC DAILY HEADACHE DETERIORATE TO THE QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Headache is common in patients with systemic lupus erythematosus (SLE). However, the lack of specific clinical distinctions for headache in SLE has made it difficult to elucidate its pathophysiology. Chronic daily headache (CDH) is a category of headache disorders that occur more than 15 days per month and associated with profound decline in quality of life. The aim of this study is to investigate the clinical chracteristics of CDH in patients with SLE and their association with the disease severity and the quality of life.
Design and Method. A total of 40 consecutive patients with SLE underwent the survey. We investigated headache characteristics, visual analogue scale (VAS) for pain, and six-question headache impact test (HIT-6) to evaluate the impact of headache on quality of life. The patients underwent required blood tests for assessment of the disease activity by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).
Results. Six patients (15%) met the criteria for CDH. The total score of HIT-6 is significantly higher in SLE patients with CDH than in them suffered from headache without CDH (p=0.027). Especially, SLE patients with CDH had more “wish could lie down” than them suffered from headache without CDH (p=0.017). The multivariate regression analysis indicated that the headache days per month was predictor for the headache-related disability.
Conclusions. As far as we know, this is the first study evaluating correlation of CDH and the quality of life in Korean patients with SLE. CDH may deteriorate to the quality of life in patients with SLE.

Key words: chronic daily headache, systemic lupus erythematosus, quality of life

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MULTIDISCIPLINARY PATIENT-ORIENTED CARE IN SYSTEMIC LUPUS ERYTHEMATOSUS: KNITTING THE REFERENCE NETWORK

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Objective. To discuss the efficiency of a horizontal referral system, including the patient organizations, for improvement of communication, quality of medical and support services, as well as research.
Design and Method. The specialists involved in the care of patients with systemic lupus erythematosus (SLE) communicate directly over every SLE patient in the referral center. This helped build an informal specialized network, through which the patients are being seen according to the principles of personalized medicine. The patient organizations are involved in this network and disseminate the information related to the disease and the specialists involved.
Results. The network approach resulted in shortened waiting times until the next specialists visits, increased patients satisfaction and reported outcomes and better enrollment into the Rheumatology Department- initiated research. It also helped strengthen connections between the medical staff and patients, between patients inflicted by the same disease as well as increase awareness on SLE within the society. Involvement of patients also brought to light a vast amount of problems not currently addressed by regular care, such as fatigue, loss of smell, medication-related weight problems, decreased social interactions etc.
Conclusions. Involvement of patient organization is crucial for building a strong network, aiming to be integrated in other European reference networks. Besides the advantages for patients, the specialists also benefit from the possibility to gather research data, with the ultimate goal to improve patient care.

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Key words: reference network, multidisciplinary approach, patient involvement

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HEMOPHAGOCYTIC SYNDROME IN SLE: A TERTIARY REFERRAL CENTER EXPERIENCE

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Objective. Hemophagocytic syndrome (HPS), a rare but life-threatening disorder, characterized by fever, macrophage activation and cytopenia, is rarely described in systemic lupus erythematosus (SLE). We aimed to retrospectively assess the episodes of overt HFS/MAS in SLE within the past five years (2011-2016) in our tertiary referral center.
Design and Method. We reviewed the medical charts of SLE patients that have met HFS criteria according to the revised HLH guidelines for lymphohystiocytosis: molecular diagnosis and/or 5/8 of the following criteria: fever, splenomegaly, cytopenia on minimum 2 blood lineages- (Hb<9 g/dl, Plt <100 x109/L, neutrophils<1x109/L), hypertriglyceridemia (>265 mg/dl) and/or hypofibrinogenemia <1.5 g/L), hemophagocytosis in bone marrow, spleen, lymph nodes or CSF with no malignancy, low/absent NK, elevated ferritin (>500 microg/L), soluble CD25/sIL2R>2400 U/ml.
Results. We identified 6 episodes of HFS in 5 SLE patients (4 F and 1 M). No patient had molecular diagnosis or testing for sCD25, but all patients fulfilled the required criteria. Bone marrow biopsy and lymph node biopsy were performed in one case. NK were found low during the episode in 3/5 patients. Infections (H. simplex- 1, Cytomegalovirus- 1, S. aureus- 1) were identified in 3/6 episodes. The episodes overlapped with an SLE flare in all cases. Antiphospholipid syndrome (APS) was associated in 4 cases (catastrophic in 2). Elevated liver enzymes and hyposodemia were constant findings. Therapy consisted in methylprednisolone

pulses, cyclosporine, anticoagulation, and if required, life support measures (CPAP ventilation- 1 case). All patients survived the HPS episodes.
Conclusions. HPS should be taken into account in SLE patients with fever and cytopenia; ferritin and lymphocyte subpopulations for NK should be assessed whenever possible in this setting. Early identification, search for infections and for associated APS and therapy with methylprednisolone and cyclosporine along with anticoagulation may improve prognosis in HPS.

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Key words: hemophagocytic syndrome, natural killer cells, ferritin

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HYPOALBUMINEMIA AND TRANSVERSE SINUS THROMBOSIS IN A PATIENT WITH SLE: A CASE REPORT

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Objective. To report a case of a 25 year old female with hypoalbuminemia, thrombosis and membranous nephropathy for which SLE with protein-losing gastroenteropathy was considered as a cause of her symptoms.
Design and Method. A 25-year-old female presents with a 7-month history of periorbital edema with no other accompanying symptoms. She was initially treated for a hypersensitivity reaction until a month prior to admission when she also developed ascites and occipital headache. She had leucopenia, positive ANA and low c3 hence a diagnosis of SLE and was given IV pulse steroids then maintained on oral steroids at a dose of 1mg/kg/day. Despite treatment, her symptoms persisted.
Results. On further work-up, she had hypoalbuminemia, a normal urinalysis and liver function tests and non-nephrotic range proteinuria. Cranial MRI with 4-vessel angiogram revealed a right transverse and sigmoid sinus thrombosis but with normal APAS panel. Renal biopsy revealed Class V lupus nephritis. Mycophenolate mofetil was started but she developed backaches and was eventually shifted to Tacrolimus. Due to the hypoalbuminemic state rendering the patient hypercoagulable in the absence of nephrotic syndrome, liver disease and malnutrition, a protein-losing enterogastropathy was considered. Multiple gastric and duodenal biopsies were taken showing normal results. In the absence of Technetium scan, serum and stool alpha1 anti-trypsin levels were requested both showing normal results.
Conclusions. In patients with SLE, hypoalbuminemia is usually secondary to nephrotic syndrome or liver disease. Protein-losing enteropathy is rare in patients with SLE and is characterized by profound edema and hypoalbuminemia. It should be suspected in the presence of persistent hypoalbuminemia with normal liver function tests, absence of significant proteinuria and adequate dietary protein intake.

Key words: systemic lupus erythematosus, transverse sinus thrombosis, hypoalbuminemia

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CALCIUM INTAKE OF ADULT POPULATION IN BOGOTA AND ASSOCIATION WITH HYPOVITAMINOSIS D. NEXT STEP: THE SAME ANALYSIS IN 100 PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOUS

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Objective. The calcium intake on the diet below normal daily requirements is related with low levels of vitamin D. We analyzed this relationship in healthy Colombian population and describe this association. After that results we are planning the same methodology to use for patients with SLE and to evaluate the impact of calcium supplementation and levels of vitamin D on the clinical course and prognostic in these patients.

Design and Method. In a prospective cohort of general population we measure the prevalence of hypovitaminosis D and the calcium intake, (mg/d) following demographic, antropomethric, biochemical characteristics and sun exposure of the population evaluated. We used a model of multiple regression to predict the levels of vitamin D regarding the factors evaluated.
The same methodology will be use in the second part of this study in our prospective cohort of 100 patients with active SLE follow up in our Institute.
Results. We included 97 patients, average age 23 yrs, 61% women, average weight 65kg, Height 165cms, BMI 22.8. The Calcium intake was 393,7mg/d, levels of vitamin D was 23.71. We identified hypovitaminosis D in 87% of the patients, deficiency in 24.7% e insufficiency in 63%.
Conclusions. We found a strong relationship between low calcium intake and hypovitaminosis D. In a healthy Colombian population we saw an important low intake of calcium on the diet and high prevalence of hypovitaminosis D.
These findings have enormous impact on public health policy in our country. Effective and imperative strategies are required to prevent future complications such as osteoporosis and secondary fractures.
There is a high prevalence of vitamin D deficiency among patients with SLE, in addition the hypovitaminosis D has been found to correlate with greater SLE disease activity. We began in the phase II of this protocol to evaluate the impact on calcium intake and measure the levels of vitamin D in patients with active SLE with the hypothesis that the course of lupus is worst in patient with both condition: Poor intake of calcium and low levels of vitamin D.

Key words: osteoporosis, hypovitaminosis D, calcium supplementation

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SYSTEMIC LUPUS ERYTHEMATOSUS COMPLICATED BY THROMBOTIC THROMBOCYTOPENIC PURPURA

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Objective. The aim of our study was to describe the clinical and pathophysiological features of Thrombotic thrombocytopenic purpura (TTP) associated with Systemic Lupus Erythematosus (SLE), in order to improve the understanding of the pathogenesis and to define a more effective treatment of this life-threatening condition.
TTP is a rare syndrome, clinically characterized by a diagnostic pentad including microangiopathic hemolytic anemia, thrombocytopenia, fever, renal involvement and neurological manifestations. TTP is generally idiopathic, but can occur in association with cancer, infections, pregnancy and also autoimmune diseases, mainly SLE. Patients (pts) with SLE who develop TTP, have a significantly poorer prognosis than those with idiopathic TTP, suggesting a possible role of other pathophysiological mechanisms of microangiopathy, in addition to defective ADAMTS13 activity. Consequently, the treatment of SLE-associated TTP can be challenging and no accepted guidelines are available at present.
Table I. Patients' clinical characteristics.

Pt	Disease duration at TTP onset	Clinical manifestations of TTP					ADAMTS13 Activity	ADAMTS13 Ab	Tx	flare	Tx 2
		A	P	K	N	F					
1	24	Y	Y	N	Y	N	Undetectable	High positive	PEX-high dose CS+AZA	no	
2	21	Y	Y	N	N	N	19%	Positive	PEX+high dose CS +CTX	6	PEX+high dose CS
3	15	Y	Y	N	Y	N	35%	Borderline	PEX+high dose CS	no	
4	14	Y	Y	Y	Y	N	14%	High positive	PEX+IVIG+ high dose CS	2	PEX+IVIG + CTX

A: anemia; P: thrombocytopenia; K: renal involvement; N: neurological involvement; F: fever; Ab: antibodies; Tx: therapy; Tx 2: therapy of flares; Y: yes; N: no; CS: corticosteroid; AZA: azathioprine; PEX: plasma exchange; CTX: cyclophosphamide; CyA: Cyclosporine A.

Design and Method. We describe the clinical and laboratory features of 4 pts with a formal diagnosis of SLE, according to the 1997 revised ACR criteria, who developed severe and acute TTP, treated with different therapeutic approaches.
Results. All the 4 pts had a long standing SLE, with a mean duration of 18,5 (14-24) years, when they develop TTP (Table I). At diagnosis, ANA was positive in all, pts 1 and 2 was anti-dsDNA positive, pts 1 and 3 had anti-SSA/Ro positivity. All pts were negative for anti-phospholipid antibodies. The immunological profile was unchanged in all pts when they had the first TTP episode, except for

anti-dsDNA that were negative in all pts. Half of them had a single episode, while the other two had several disease flares during steroids tapering, that was very difficult to control. In both these cases, long term remission was obtained with full dose (2-3 gr daily) of mycophenolate mofetil (MMF) and flares occurred when MMF dosage was reduced. Pt 2 is now on remission on MMF 3 grams daily, while pt 4 had gastrointestinal side effects with full dose MMF; thus, belimumab and low dose cyclosporine was added to MMF 1 gr daily, without reactivation of TTP.
Conclusions. TTP represents a rare but very severe complication of SLE. Even if in our cohort the pathophysiological mechanisms leading to the disease seemed to be coincident with those of classical idiopathic TTP, a complete control of the disease can be very difficult to achieve and flares of microangiopathic are not uncommon during the tapering of steroids and immunosuppressant. An aggressive therapy with multiple drugs is usually needed to maintain remission.

Key words: systemic lupus erythematosus, TTP, mycophenolate mofetil

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LIMBIC ENCEPHALITIS IN A SLE PATIENT WITH PAPILLARY THYROID CARCINOMA

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Objective. Limbic Encephalitis (LE) is an uncommon manifestation of Systemic Lupus Erythematosus (SLE). It can also be of paraneoplastic etiology, sometimes preceding the tumor identification.
Design and Method. The authors describe a case of LE in a patient with a history of SLE in which a diagnosis of papillary thyroid cancer was made.
Results. A 45-year-old woman with a history of SLE (ANA+, anti-DsDNA-) with previous renal and mild articular and hematological involvement, in remission with hydroxicloroquine, presented to the emergency room with generalized tonic-clonic seizures after a week of flu-like symptoms. A lumbar tap showed only discrete lymphocytic pleocytosis; cerebrospinal fluid ANAs were negative. The brain magnetic resonance imaging (MRI) was normal. A presumptive diagnosis of meningitis was made and antibiotic therapy was started. Two days later the patient started a non-convulsive status epilepticus and was transferred to an intensive care unit. Electroencephalogram (EEG) showed frequent paroxysmal activity at medial-parietal topography in the right hemisphere. A second brain MRI revealed changes suggestive of LE and on this moment cerebrospinal fluid showed not only an increase in the number of cells but also protein synthesis. Anti-epileptic drugs were started and a methylprednisolone pulse was administrated, followed by intravenous cyclophosphamide and immunoglobulin with good response. Additional investigation included NDMA, GABA, AMPA, VGKC, and anti-neuronal antibodies antibodies, which were all negative. To further investigate a paraneoplastic etiology, a CT scan was performed, which led to the diagnosis of a solid thyroid lesion. By fine-needle aspiration a diagnosis of papillary thyroid carcinoma was made.
Currently, after 6 weeks of treatment, the patient is stable and without seizures. As neurological sequelae she kept a slight dysmnesia and an attention deficit. Thyroidectomy has been scheduled.
Conclusions. Besides the rarity of this case it also presents a major diagnostic challenge as the etiology of LE remains unclear being possible the responsibility of SLE but also the paraneoplastic etiology. These two features make of it a case to report and discuss.

Key words: limbic encephalitis, thyroid carcinoma, lupus

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SLE IN MALES- SHORT CASE SERIES - MEN MAY HAVE MORE NEUROLOGICAL DISEASE!

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Objective. SLE is a multisystem autoimmune disorder. The prevalence is estimated to be 20-70/100,000 people worldwide (1). It's progression is determined by the hormonal, genetic and environmental factors (2) (3). The disease tends to be more prevalent in non-white population than the whites (4). It is also found to be more severe in males (5). This case series will help identify these gender variations in SLE its impact on morbidity. This short review is a part of larger study of patients with SLE in South India.
Design and Method. This retrospective observational study was conducted at Velammal Medical College Hospital and Research Institute, Madurai, South India. All patients with SLE were reviewed over a 3-month period and the 4 males (4 out of 14 SLE) have been extensively studied in this series. All of them had the diagnosis of SLE by the Rheumatologist and followed up. Appropriate imaging and immunology were done.
Results. This review shows incidence of SLE in males higher.

Characteristics	Patient P	Patient V	Patient MK	Patient MA
CLINICAL FEATURES				
Mucocutaneous	Rash, Hair loss	Mouth ulcers	Mouth ulcers	Mouth ulcers
Muskuloskeletal	Aethalgia	Rash, DLE	Knee Ankle synovitis	back pain
Renal	No	Proteinuria	Proteinuria	Nephritic, V
CNS	Chorea	Headache	Acute psychosis	Headache
Constitutional	Fatigue, Fever	Enlarged nodes	Fever, Weight loss	Fever
Others	Foot drop	Partches	Pulmonary hypertension	Sacroileitis
IMMUNOLOGY				
ANA	1 in 320	1 in 640	1 in 2560	1 in 320
ENA	Sm, RNP positive	Ro positive	Ro positive	Sm
C3/C4	Low C3 and C4	Normal	Low C3	Low C3
Ds DNA	Positive	Positive	Normal	Positive
COMPLICATIONS				
Renal	None	None	None	Nephrotic, V
Neurological	Chorea, Foot drop	None	Psychosis	None

Conclusions. Our case series shows higher incidence of SLE in males. Men have more musculoskeletal and cutaneous features, systemic involvement is mild with renal disease and more of neurological system, which is in contrast to the literature. Asian cohort behaves differently compared to the Caucasians and Africans. Immunology correlates well with clinical features like Sm antibody (renal disease), Ro antibody (cutaneous disease) and ribosomal P antibody (neurological disease). While some researchers have implicated central nervous system involvement (6) in contributing to a poor prognosis, others have not. Long-term follow up will enlighten us more
SLE in males manifest with clinical, immunological and systemic features quite different, compared to females. Our series show men may present with more neurological involvement and mild renal disease. Further studies are ongoing to review wider cohort in SLE. With the advancement of immunological evaluation, more and more SLE diagnosis are coming up.

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Key words: SLE, male, ribosomal P antibody

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FAMILIAL COLD AUTOINFLAMMATORY SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS: A PUZZLING ASSOCIATION

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Objective. Familial cold autoinflammatory syndrome (FCAS) is an autoinflammatory disease in which exposure to cold triggers a systemic inflammatory reaction. We aim to describe an unusual association of FCAS with SLE, resulting in delayed diagnosis and other clinical implications.
Design and Method. -
Results. A 24-year-old patient with a maternal history of "cold intolerance" presented 15 years ago with intense inflammation (ESR 85 mm/h), leukocytosis (11500 WBC/microl), fever, urticarial rash, conjunctival injection, intense arthralgias, headaches and myalgias, without a clear relation to a certain exposure. An extensive search for an infection and associated autoimmune disease were unsuccessful. Cryoglobulins, cryoagglutinins and cryofibrinogen were negative. The episode was recurrent, not alleviated by colchicine, but by short courses of prednisone instead, and was self-limited at times. An autoinflammatory disease (familial Mediterranean fever, having in view the short duration of episodes, or TRAPS due to the prominent conjunctivitis) were suspected by then. IgD was normal; a muscle biopsy identified a macrophagic myositis without amyloid deposition. The genetic testing was not possible. The detection of antinuclear antibodies after a few months was puzzling, and the occurrence of pericarditis, photosensitivity, splenomegaly and persistent wrist arthritis (with overlapping self-limited joint flares) added to the SLE criteria in this setting. However, cytopenias were never found during the disease. After finding of other familial cases of cold-induced urticaria, the diagnosis of FCAS was retained. Over time, the antinuclear antibody profile was mostly anti-Ro. No interstitial lung involvement was found, and muscle enzymes were normal. Apart from hydroxychloroquine and cyclosporine, no other second-line therapy was tolerated. The main type of SLE-related involvement was articular and cutaneous, while the persistent urticarial rash, conjunctivitis and mild neurosensorial hypoacusis were likely the consequence of FCAS. Anti-IL-1 therapy was not available.
Conclusions. An underlying autoinflammatory disease may modify the SLE presentation and clinical picture, resulting in paroxistic self-limiting features like pericarditis, bouts of arthritis and skin rashes that could be mistaken for SLE flares.

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Key words: autoinflammatory, FCAS, anti-Ro.

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NEONATAL LUPUS ERYTHEMATOSUS PRESENTING WITH HEART BLOCK AND PNEUMONITIS: A DIFFICULT CASE

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Objective. Neonatal lupus erythematosus (NLE) is a rare auto-immune condition of neonates related to the transplacental passage of maternal autoantibodies (anti-SSA, SSB and rarely anti-U1RNP) to the foetus after the 16th week of gestation leading to lesions in target organs. The most common findings include skin lesions and/or congenital heart block. Other systemic features as pneumonitis have been occasionally documented. Our aim is to describe a case of acute lupus pneumonitis in a newborn with NLE.
Design and Method. The authors present the case of a boy born to a 35-year-old mother with systemic lupus erythematosus with positivity for anti-SSA and anti-SSB, and a previous child with NLE with congenital complete heart block who died at the age of two due to myocarditis. The pregnancy was surveilled, the mother was treated with prednisolone and hydroxychloroquine and a prenatal diagnosis of congenital complete atrioventricular block was made. The mother received dexamethasone and salbutamol but refused endovenous immunoglobulin and plasmapheresis.
Results. The child was born during the 36th week of gestation, by cesarean, with an Apgar 1´/5´of 9/10 and admitted to the Department of Neonatology. 24 hours after birth a temporary pacemaker was inserted, which was only replaced by a definitive pacemaker when the patient was 14 days old due to concurrent sepsis. At D22 he developed hypoxemic acute respiratory failure requiring mechanical ventilation. Chest radiographs showed diffuse bilateral cotton-like infiltrates and lung CT revealed ground glass opacities. In the following 48 hours there was clinical worsening, despite broad-spectrum antibiotics, absence of fever, negative cultures and progressive normalization of leukocyte count and C-reactive protein level. The immunology panel showed positivity for antinuclear antibodies at titer 1/320 (speckled pattern), positivity for antibody anti-SSA and also anti-dsDNA, with absence of anti-SSB, anti-RNP. The clinical picture was interpreted as NLE-related pneumonitis and the patient received intravenous methylprednisolone pulses (30 mg/kg/day) on 3 consecutive days, followed by oral prednisolone in progressively lower doses, with excellent clinical and imagiological response.
Conclusions. This case represented a challenge as pulmonary manifestations presented in a neonate with NLE with congenital heart block that was being treated for neonatal sepsis. Besides the rarity of NLE-related pneumonitis, treatment with corticosteroids had a lot of risks in this patient. However, the imagiological and immunological findings and the fact that there was a good response to corticotherapy and not to broad spectrum antibiotics made this diagnosis the most probable, with a successful outcome.

Key words: neonatal lupus erythematosus, pneumonitis, treatment

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ROLE OF NEUROIMAGING IN REFRACTORY NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (NPSLE)

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Objective. To describe the emblematic role of brain Magnetic Resonance Imaging (bMRI) in a difficult clinical case of NPSLE.
Design and Method. A 58-year-old Professor with a known history of seizures and hemochromatosis, was diagnosed with NPSLE and Antiphospholipid Syndrome (APS) according to ACR criteria.
Results. bMRI showed a number of white (WMHI) and gray matter (GMHI) T2-hyperintense lesions in sovra- and sub-tentorial regions and a bigger lesion in the right parietal lobe with a dishomogeneous peripheral contrast-enhancement, which was thought to be an inflammatory-like lesion. No other causes were found. He was treated with steroids, antiplatelets therapy, Hydroxychloroquine and Micophenolate Mofetil with stable clinical conditions for 6 years. In 2014 he came firstly to our hospital complaining worsening in dizziness, dysphagia and emotional lability. A new bMRI showed a numerical increase in WMHI (in periventricular WM of cerebral hemispheres); lesions in left lenticular nucleus and corona radiata showed restricted diffusion. The lesion in the parietal lobe was unmodified in size, confirming peripheral gadolinium-enhancement: these characteristics were more suggestive of a benign heteroplastic lesion (ganglioglioma) instead of an inflammatory lesion. Analysis of cerebrospinal fluid (CSF) was collected with no pathologic features. He was treated with high dose Intra Venous Immunoglobulin and with IV Cyclophosphamide (6 grams). Despite this treatment he complained an acute worsening with left hemiparesis and spatio-temporal disorientation. Neuroimaging showed an increased lesion-load in periventricular WM and in cerebellar right hemisphere. T1-hyperintensities were identified in basal ganglia and in subcortical area of right parietal lobe (microbleedings). A new contrast-enhanced lesion appeared in left cerebellar hemisphere. During following months signs of initial dementia became clear, with archaic reflexes appearance in neurologic examination and verbal circumlocutions; short-term amnesia and urinary incontinence also occurred. In this refractory organic brain syndrome lupus-related a therapeutic approach with weekly-regimen of plasmapheresis, pulse steroids and subsequently Rituximab treatment was adopted. Heparin was also started instead of anticoagulant therapy due to presence of microbleedings. In the last six months there was a mild improvement in mental function and motor ability; dysphagia and urinary continence were restored. The last bMRI was stable compared to previous.
Conclusions. Conventional bMRI could help clinician in assessing activity of NPSLE and guide the correct therapeutic approach in refractory cases; sequential neuroimaging assessment is mandatory during follow up.

Key words: neuropsychiatric, lupus, neuroimaging

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A RAPID SEQUENCE OF EVENTS

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Objective. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, with a broad range of clinical presentations and also a wide spectrum of severity having some, although rare, cases a fatal disclosure. Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immune overstimulation. It can be primary, when associated with genetic defects or secondary to malignancy, infection or autoimmune diseases like SLE.
Design and Method. The authors present a 27-year-old-man, with no previous medical history that presented to our medical department complaining of fever, arthralgia, weight loss, malar rash and oral ulcers, with only two weeks of evolution. After being admitted, he experienced a rapid sequence of clinical events with severe renal, hematologic and neurologic involvement overcoming and resulting in the admission in the intensive care unit (ICU) with the need of mechanical ventilation.
Results. SLE, with multisystemic involvent, was assumed and a secondary HLH was equated. On this context and, besides high dose corticosteroids, aggressive immunosuppressive treatment with intravenous cyclophosphamide was started conducting to a slow but significative recovery. Seven months afterwards the patient has no symptoms. Having completed nine cyclophosphamide infusions azathioprine was started. The corticosteroid dosage was slowly reduced to 6mg of deflazacorte. Besides these drugs he is also under hydroxychloroquine.
Conclusions. Our case is paradigmatic of the importance of a prompt recognition and aggressive treatment of severe SLE in order to avoid progression that sometimes leads to death. The hypothesis of secondary HLH emphasized this need in our patient. We report this case not only to remark the rarity of its presentation but also to ilustrate that an aggressive aproach can be lifesaving in this context and should not be delayed.

Key words: hemophagocytic lymphohistiocyte, intensive care unit, cyclophosphamide

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SKIN CANCER IN A COHORT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Conflicting results about the incidence of skin cancer in Systemic Lupus Erythematosus (SLE) have been reported in the literature (1, 2). The aim of our study was to retrospectively evaluate the incidence of malignancies in a cohort of patients with SLE in a single center.
Design and Method. All the SLE patients classified according to ACR and SLICC criteria, attending our center were retrospectively evaluated. Clinical and laboratory data were obtained from clinical charts. Diagnoses of skin cancer (melanoma and non-melanoma:basalioma,squamous cell carcinoma) and other malignancies were recorded together with SLE disease duration. Univariate analysis was performed to compare the characteristics of patients with and without cancer. We also compared the incidence of cancer in our population to that of the italian general population (from the Italian national institute of statistics report 2014).
Results. In a cohort of 509 SLE patients (92% Females, 95% Caucasian) regulary followed from 1972 to 2016 (mean age at diagnosis 32.5 years ± 13 and median follow-up 12 years,range 1-40) we detected 3 patients with melanoma (0.5%), 13 with non-melanoma skin cancer (2.5%) and 74 with other malignancies (14.5%). The mean SLE disease duration at the time of cancer diagnosis was 10 years. Table I reports the comparison between patients with and without skin cancer. The incidence rate of non skin cancer was 1.1% in SLE compared to 0.06% patient-year in the general italian adult population, whereas the rate of non-melanoma skin cancer was 0.02% compared to 0.01% respectively.

Table I. Characteristics of Systemic Lupus Erythematosus patients with and without cancer.

Variable	All patients (n=509)	Patients without cancer (n=419)	Patients with cancer (n=90)	M (n=3)	Non M (n=13)	Others (n=74)	*p* value*
Female sex, n (%)	469 (92)	383 (91)	86 (96)	3 (100)	13 (100)	70 (95)	0.18
Caucasian ethnicity, n (%)	482 (95)	396 (94)	86 (95)	3 (100)	13 (100)	70 (95)	0.68
Age at SLE diagnosis, years, mean (SD)	32 (13)	31 (12)	37 (13)	21 (1)	42 (17)	3(12)	<0.0001
Age at cancer diagnosis, years, man (SD)	NA	NA	37 (13)	33 (4)	49 (18)	46 (13)	NA
Disease duration at cancer diagnosis, years, median (range)	NA	NA	8 (1-35)	14 (8-16)	7 (1-27)	8 (1-36)	NA
SLE skin involvement, n (%)	295 (58)	237 (56)	51 (57)	1 (33)	5 (38)	42 (57)	0.98
Photosensitivity, n (%)	244 (48)	209 (50)	35 (39)	1 (33)	5 (38)	24 (32)	0.06
Positivity for ANA, n (%)	496 (97)	409 (98)	85 (94)	3 (100)	12 (92)	70 (95)	0.50
Positivity for anti-ds DNA, n (%)	438 (86)	361 (86)	74 (82)	3 (100)	12 (92)	59 (80)	0.88
Positivity for antiENA, n (%)	295 (58)	248 (59)	46 (51)	2 (67)	6 (46)	38 (51)	0.20
Complement reduction n (%)	186 (36)	153 (36)	32 (35)	1 (33)	4 (31)	27 (36)	0.97

M: Melanoma; NonM: Non-Melanoma; Other: Other malignancies; SLE: Systemic Lupus Erythematosus; ANA: Anti-Nuclear Antibody; antiENA: Anti-Extractable Nuclear Antigen; anti-ds DNA: anti-Double stranded DNA; SD: standard deviation; NA: not applicable.
*comparison of patients without cancer versus patient with cancer.

Conclusions. The incidence of cancer in our SLE cohort was increased in comparison to the general population. Non-melanoma was the most common skin cancer in our SLE cohort. Skin cancers represented a minority of neoplasms as reported in the general population. The mean age at cancer diagnosis was 46 years. Patients developing malignancies were significantly older when SLE was diagnosed. Nevertheless, patients with melanoma were significantly younger compared to every other group of patient either without malignancies or with non skin malignancies or with non-melanoma skin cancer. No other associated features were detected.

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Key words: systemic lupus erythematosus, cancer, skin

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COLLAGEN INDUCED ARTHRITIS (CIA): A MURINE MODEL TO EVALUATE THE ROLE OF SERPINB3 IN PREVENTION AND TREATMENT OF ARTHRITIS IN AUTOIMMUNE DISEASES

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Objective. Collagen induced arthritis (CIA) is one of the most studied murine model for arthritis in a large spectrum of different autoimmune diseases such as lupus erythematosus systemic (SLE), rheumatoid arthritis (RA) and others. The aim of our study was to assess the effect of SerpinB3 in the treatment of CIA in Balb/c mice.

Materials and Methods. The murin model was made up by thirty mice subdivided into three different groups of ten each. The first group was injected with 15 μg of SerpinB3 the day before the CIA induction (preventive approach); then, the second group was injected with 15 μg of SerpinB3 starting when mice developed a CIA severity score ≥2 (therapeutic approach); finally, the control group was injected with PBS when mice developed a CIA severity score ≥2.

Results. Compared with controls, mice treated with preventive approach, belonging to the first group, had lower median scores of CIA severity in all the 18 weeks of treatment ($p<0.0001$ for all) and lower limb swelling measures after 11 weeks of treatment (week 12: $p=0.007$, weeks 14 and 17: $p=0.003$, week 15: $p=0.045$, week 16: $p=0.043$, weeks 13 and 18: $p<0.0001$). All control mice but none of the preventive approach group developed walking and strength impairment. In the therapeutic approach group, the median scores were similar to controls in the first 3 weeks of treatment, thereafter these scores became significantly lower than PBS treated mice (weeks 4, 5 and 7: $p=0.007$, week 6: $p=0.003$, weeks 10, 11 and 12: $p= 0.001$, from week 13 to week 18: $p<0.0001$). No significant differences were observed in the limb swelling measures between therapeutic approach group and controls. Two mice of the therapeutic approach group showed walking and strength impairment.

Conclusions. It was demonstrated that the administration of SerpinB3 in a murin model of CIA attenuates the onset and the progression of arthritis.