S1: Hormones and environments in SLE

S1:03

ALL DISEASE BEGINS IN THE GUT: CELIAC DISEASE CO-EXISTENCE WITH SLE

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Objective. Background: Case reports and case series have indicated a possible association between celiac disease (CD) and systemic lupus erythematosus (SLE), but additional population-based studies are required. Our objective was to investigate the association between CD and SLE.

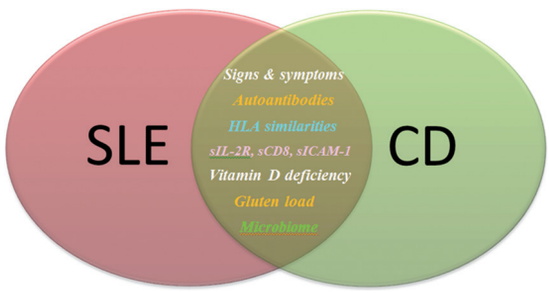

Fig. 1. Emerging evidence point to a link between SLE and CD. (SLE: Systemic Lupus Erythematosus; CD: Celiac Disease).

Design and Method. Methods: Patients with SLE were compared with age- and sex-matched controls regarding the prevalence of CD in a case-control study. Chi-square and t-tests were used for univariate analysis and a logistic regression model was used for multivariate analysis. The study was performed utilizing the medical database of Clalit Health Services.
Conclusions. The study included 5,018 patients with SLE and 25,090 age- and sex-matched controls. The prevalence of CD was significantly higher in patients with SLE than in controls in univariate analysis (0.8% and 0.2%, respectively, $p<0.001$). Also, SLE was associated with CD (OR 3.92, 95% CI 2.55 – 6.03, $p<0.001$) in a multivariate logistic regression model.

Key words. systemic lupus erythematosus, celiac disease, autoimmunity

S1:04

HELMINTHES RELATED TUFTSIN-PHOSPHORYLCHOLINE COMPOUND: SUCCESSFUL TREATMENT OF MURINE LUPUS NEPHRITIS AND ITS EFFECT ON THE MICROBIOTA

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Objective. The "hygiene hypothesis" suggests that sanitizing the environment leads to an increased incidence of autoimmune diseases. There is a significant correlation between the presence of helminthes in certain geographic areas and protection from autoimmune diseases. Treatment with helminthes and their ova, improved clinical findings of inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis. The immunomodulatory functions of some helminths were attributed to the phosphorylcholine (PC) moiety. We aimed to decipher the tolerogenic potential of Tuftsin-PC (TPC) compound in mice genetically prone to develop lupus when the disease was already established. In addition we analyzed the microbiota, assuming that it may be affected by TPC treatment on lupus development
Design and Method. NZBxW/F1 lupus prone mice received subcutaneously TPC, 3 times a week starting at 24 weeks of age, when proteinuria showed 10 mg/dl. At this point feces were collected weekly. Autoantibodies were tested by ELISA, in-vitro cytokines secretion by DuoSet ELISA, T-regulatory-cells by FACS. Glomerulonephritis was addressed by detection of proteinuria, and immunoglobulin complex deposition in the mesangium of the kidneys by immunofluorescence. Stools from the mice were collected every 3 days for microbiome analyses. DNA was extracted from the stools and then sequenced using Illumina Miseq platform. Data analysis was performed using QIIME.
Results. Our results show that TPC treatment attenuated the development of glomerulonephritis in lupus prone mice, manifested by reduced proteinuria and immunoglobulin deposition in the kidney mesangium. TPC also increased the expression of IL-10 ($p<0.001$), and inhibited the production of IFNgamma, IL-1beta and IL-17 ($p<0.03$). TPC significantly expanded $CD4^+CD25^+FOXP3^+$ T-regulatory cells (Tregs) phenotype in the treated mice. The microbiota analyses showed that TPC exhibited a marked depletion of Akkermansia (specifically muciniphila species) and higher abundance of Odoribacter compared to PBS treated mice, which correlated to proteinuria levels. Generally, high protein secretions correlated with an increased abundance of four bacteria genera; Akkermansia AF12, S24-7, Bacteroides, and one bacteria order Clostridiales. High protein levels were correlated also with decreased levels of thirty-three additional otus, with the Odoribacter genus among them.
Conclusions. Our data indicate that TPC treatment inhibits lupus nephritis development in genetically lupus prone mice, attenuates pro-inflammatory cytokines and enhance anti-inflammatory IL-10 expression, as well as Tregs expansion. The results propose harnessing novel natural therapy for lupus patients. In addition our results show that TPC significantly alters the microbiota composition which correlated with decreased protein levels in the urine.

Key words: lupus mice, helminthes, microbiome

S1:05

SERUM ANTI-MÜLLERIAN HORMONE LEVELS IN SLE PATIENTS: INFLUENCE OF DISEASE SEVERITY AND THERAPY ON THE OVARIAN RESERVE

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Objective. Systemic lupus erythematosus (SLE) predominantly affects women of reproductive age and may negatively affect their fertility due to severe organ involvement and the prolonged immunosuppressive therapy used. The Anti-Müllerian Hormone (AMH) is secreted from granulosa ovary cells and serum levels of Anti-Müllerian Hormone are used as a measure of ovarian reserve, reflecting the number of primary follicles. The purpose of this study is to compare serum levels of AMH in a cohort of patients with SLE and healthy controls and to assess whether the presence of the disease, the treatments used and/or other clinical parameters may affect the ovarian reserve.
Design and Method. Eighty-six consecutive female patients with SLE of childbearing age, aged between 18 and 42 years and with regular menses and 44 healthy controls age-matched were evaluated. Anti-Müllerian Hormone levels were measured in peripheral blood samples (kit AMH Gen II ELISA, Beckman Coulter). Clinical and demographic characteristics, disease duration, pattern of organ involvement and previous and current therapies were collected at the time of sampling. Fourteen patients (16.3%) had been treated with cyclophosphamide (CTX, cumulative dose 8.3±5.4 g), and of the remaining, 39 (45.3%) with other DMARDs (methotrexate, azathioprine, mycophenolate mofetil, cyclosporine) and 33 (38.4%) with anti-malarials only.
Results. Patients with SLE had a mean age of 30.4±6.3 years, a disease duration of 7.7±5.1 and 25 patients (33.3%) had a severe organ involvement (mainly renal and neurological, 14 were treated with cyclophosphamide, 11 with other DMARDs). Serum levels of AMH were comparable between patients and controls (4.2±3.3 vs 5.0±3.1 ng/ml, respectively, $p=0.2$). Considering patients on the basis of organ involvement, patients with major organ involvement had AMH levels (3.6±2.8 ng/ml) significantly lower than control subjects ($p=0.03$); no difference was found between patients with minor organ involvement (AMH 4.4±3.4 ng/ml) and control subjects ($p=0.4$). Considering the treatments used, patients with major organ involvement treated with cyclophosphamide showed serum AMH levels lower than controls (2.9±3.3 ng/ml, $p=0.06$). There were no associations between the use of other DMARDs than cyclophosphamide and lower AMH levels in SLE patients compared to controls.
Conclusions. In the whole cohort of SLE patients, the ovarian reserve was overall comparable to that of healthy controls, whereas a reduction of the ovarian reserve was associated with the use of cyclophosphamide and the severity of the disease.

Key words: ovarian reserve, anti-Mullerian hormone, cyclophosphamide.

S2: Belimumab, rituximab and other targeted therapy

S2:03

ANIFROLUMAB, AN ANTI-INTERFERON-ALPHA RECEPTOR MONOCLONAL ANTIBODY, IN MODERATE TO SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Objective. The efficacy and safety of anifrolumab, a type I interferon (IFN) receptor antagonist, were assessed in a Phase IIb, randomized, double-blind, placebo-controlled study of adults with moderate to severe SLE (the MUSE study).
Design and Method. 305 patients were treated for 48 weeks with intravenous anifrolumab (300 mg, 1000 mg) or placebo, in addition to standard-of-care medications. Randomization was stratified by baseline SLE Disease Activity Index 2000 (SLEDAI-2K) score (<10 or ≥10), oral corticosteroid (OCS) dose (<10 or ≥10 mg/day), and IFN gene signature status (high vs. low) based on a 4-gene expression assay. The primary endpoint was the percentage of patients achieving an SLE Responder Index [SRI(4)] response at Day 169 with sustained reduction of OCS (<10 mg/day and ≤ Day 1 dose from Day 85 to 169).
Results. The primary endpoint was met. Treatment effect sizes were greatest in patients with a high baseline IFN signature (table). At Day 365 anifrolumab-treated patients achieved greater responses in SRI(4), BILAG-based Composite Lupus Assessment (BICLA), modified SRI(6), SLEDAI-2K ≤2, and major clinical response (BILAG "C" or better in all domains at Day 169 maintained to Day 365). BILAG "A" flares were reported in more placebo- vs. anifrolumab-treated patients. In patients with baseline Cutaneous Lupus Erythematosus Disease Area and Severity Index activity scores ≥10, more anifrolumab-treated patients attained ≥50% reduction by Day 365. In patients with ≥8 swollen and ≥8 tender joints at baseline more anifrolumab-treated patients achieved ≥50% decrease in both swollen and tender joint count. The observed benefits were driven by the IFN-high subpopulation, which comprised 75% of the cohort. Median suppression of 21 IFN-regulated genes was ~90% for both doses of anifrolumab. Compared with placebo a higher percentage of anifrolumab-treated patients had *Herpes zoster* (2.0%, 5.1%, 9.5%) and cases reported as influenza (2.0%, 6.1%, 7.6%). There were no differences in the incidence of serious adverse events (18.8%, 16.2%, 17.1%). The incidence of infusion-related reactions was similar (5.9%, 2.0%, 3.8%).

Table. Efficacy results

	Placebo (n=102)	Anifrolumab 300 mg[a] (n=99)	*P*-Value	Anifrolumab 1000 mg[a] (n=104)	*P*-Value
Day 169					
SRI(4) (including OCS taper)	17.6	34.3	0.014	28.8	0.063
IFN high	13.2	36.0	0.004	28.2	0.029
IFN low	30.8	29.2	0.946	30.8	0.953
Day 365					
SRI(4) (excluding OCS taper)	40.2	62.6	<0.001	53.8	0.043
BICLA	25.7	53.5	<0.001	41.2	0.018
mSRI(6)	28.4	49.5	0.002	44.7	0.015
SLEDAI-2K ≤2	17.6	35.4	0.004	32.7	0.012
Major clinical response[b]	6.9	19.2	0.012	17.3	0.025
BILAG "A" flares	16.7	9.1	0.134	10.6	0.253
≥50% improvement in CLASI[c]	30.8	63.0	0.013	58.3	0.077
≥50% improvement in joint counts[d]	48.6	69.6	0.038	64.6	0.156
Meeting OCS taper criteria[e]	26.6	56.4	0.001	31.7	0.595

[a]Every 28 days from Day 1 to Day 337. [b]BILAG "C" or better in all organ domains at Day 169 with maintenance of this response through Day 365. [c]≥50% decrease from baseline in patients with CLASI activity score ≥10 at baseline. [d]≥50% decrease in swollen and tender joint count from baseline in patients with ≥8 swollen and ≥8 tender joints at baseline. [e]Reduction of OCS dosage to ≤7.5 mg/day in patients who were receiving ≥10 mg/day at baseline. BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; mSRI, modified SLE responder index; OCS, oral corticosteroid; SLEDAI–2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI, Systemic Lupus Erythematosus Responder Index

Conclusions. Anifrolumab significantly reduced disease activity across all clinical endpoints. Enhanced effects in IFN-high patients support the pathobiology of this treatment strategy.

Funded by MedImmune. Editorial assistance: K Alexander, QXV Comms, an Ashfield business, UK

Key words: Efficacy, Clinical trial, Low disease activity.

S2:04

ANIFROLUMAB REDUCES DISEASE ACTIVITY IN MULTIPLE ORGAN DOMAINS IN MODERATE TO SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Objective. As reported elsewhere, anifrolumab was evaluated in a Phase IIb study of SLE patients with moderate to severe disease activity, in which 305 patients received intravenous anifrolumab (300 mg, 1000 mg) or placebo for 48 weeks. Both doses reduced global disease activity, although a more favorable risk-benefit profile was observed with the 300-mg dose. This analysis compared the impact of anifrolumab on individual organ domains in patients with moderate to severe SLE who participated in the Phase IIb study.
Design and Method. At Week 52 changes from baseline in organ domain activity were assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) and British Isles Lupus Assessment Group (BILAG). Improvement in a SLEDAI domain required a lower score at Week 52 compared with baseline in at least one of its components. Improvement in a BILAG organ domain was defined as the transitioning from "A" or "B" to a lower score.
Results. The majority of patients had baseline involvement of the mucocutaneous and/or musculoskeletal domains of SLEDAI-2K and BILAG. Compared with placebo, a greater percentage of patients in the anifrolumab-treated groups improved in these frequently involved domains (table). Trends suggesting potential benefits were observed in most of the other less frequently active domains, including SLEDAI-2K cardiorespiratory, vascular, hematological, and constitutional; and BILAG cardiorespiratory and constitutional domains. Of those patients who had involvement in the SLEDAI-2K immunological domain at baseline (positive anti–double-stranded DNA [anti-dsDNA] and/or low complement level), greater numbers of patients in the anifrolumab groups had lower scores at Day 365 (table), representing a normalization of anti-dsDNA and/or hypocomplementemia. However, among patients who had a normal anti-dsDNA and/or normal complements at baseline, a slightly greater number of patients treated with 300-mg anifrolumab had an increase in the score representing the development of a new anti-dsDNA or hypocomplementemia compared with baseline (table).

Table. Changes from baseline in organ domain activity at Day 365

	Placebo	Anifrolumab 300 mg[a]	*P*-Value	Anifrolumab 1000 mg[a]	*P*-Value
Organ domain improvement at Day 365					
BILAG, n (%)					
Mucocutaneous	24/87 (27.6)	49/84 (58.3)	<0.001	33/82 (40.2)	0.069
Musculoskeletal	47/95 (49.5)	64/94 (68.1)	0.005	54/91 (59.3)	0.149
SLEDAI-2K, n (%)					
Mucocutaneous	38/100 (38.0)	61/99 (61.6)	<0.001	51/102 (50.0)	0.082
Musculoskeletal	42/99 (42.4)	55/97 (56.7)	0.032	50/98 (51.0)	0.197
Immunological	4/53 (7.5)	9/43 (20.9)	0.068	18/59 (30.5)	0.004
Organ domain worsening at Day 365					
SLEDAI-2K, n (%)					
Immunological	7/79 (8.9)	11/82 (13.4)	-	6/79 (7.6)	-

[a]Every 28 days from Day 1 to Day 337. BILAG, British Isles Lupus Assessment Group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

Conclusions. Anifrolumab treatment resulted in greater rates of improvement than placebo in multiple organ domains, with greatest impact seen with 300-mg anifrolumab.

Funded by MedImmune. Editorial assistance: K Alexander, QXV Comms, an Ashfield business, UK.

Key words: novel therapy, interferon, efficacy

S2:05

CONTINOUS REGENERATION OF LONGLIVED MEMORY PLASMA CELLS IN MURINE SLE REQUIRES A COMBINED DEPLETION OF PLASMA CELLS AND THEIR PRECURSORS

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Objective. Autoantibodies contribute significantly to the pathogenesis of systemic lupus erythematosus (SLE). Unfortunately, the long-lived memory plasma cells (LLPCs) secreting such autoantibodies are refractory to conventional immunosuppressive treatments. Although generated long before the disease becomes clinically apparent, it remains rather unclear whether LLPC generation continues in the established disease. Here, we analyzed the generation of LLPCs, including autoreactive LLPCs, in SLE-prone New Zealand Black/New Zealand White F1 (NZB/W F1) mice over their lifetime, and their regeneration after depletion.
Design and Method. Bromodeoxyuridine pulse-chase experiments in mice of different ages were performed in order to analyze the generation of LLPCs during the development of SLE. LLPCs were enumerated by flow cytometry and autoreactive anti-double-stranded DNA (anti-dsDNA) plasma cells by enzyme-linked immunospot (ELISPOT). For analyzing the regeneration of LLPCs after depletion, mice were treated with bortezomib alone or in combination with cyclophosphamide and plasma cells were enumerated 12 hours, 3, 7, 11 and 15 days after the end of the bortezomib cycle.
Results. Autoreactive LLPCs are established in the spleen and bone marrow of SLE-prone mice very early in ontogeny, before week 4 and before the onset of symptoms. The generation of LLPCs then continues throughout life. LLPC counts in the spleen plateau by week 10, but continue to increase in the bone marrow and inflamed kidney. When LLPCs are depleted by the proteasome inhibitor bortezomib, their numbers regenerate within two weeks. Persistent depletion of LLPCs was achieved only by combining a cycle of bortezomib with maintenance therapy, for example cyclophosphamide, depleting the precursors of LLPCs or preventing their differentiation into LLPCs.
Conclusions. In SLE-prone NZB/W F1 mice, autoreactive LLPCs are generated throughout life. Their sustained therapeutic elimination requires both the depletion of LLPCs and the inhibition of their regeneration.

Key words: plasma cells, depletion, regeneration

S2:06

RITUXIMAB FOR SLE REFRACTORY TO CONVENTIONAL TREATMENT: RESULTS OF A COHORT EVALUATING EFFICACY AND LONG-TERM OUTCOME

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Objective. To determine the efficacy and safety of treatment with rituximab (RTX) in patients with active SLE who had an inadequate response to standard treatment.
Design and Method. RTX was administered in 26 cases (25 patients) in our Department over the last 8 years. All patients (23 women, 2 men with a median age 33yr (range14-66 yr) had active SLE despite standard treatment. Outcome measures were improvement in signs and symptoms during a follow-up period of at a mean of 5 years.
Results. The clinical manifestations of these patients at the time of RTX administration included: proliferative nephritis in 9 patients, articular involvement in 3 patients, mucocutaneous involvement in 2 patients, heamatologic abnormalities in 3 patients, central nervous system involvement in 5 patients, pulmonary involvement in 3 patients, vasculitis in 3 patients and a plasmapheresis plus steroid resistant case of TTP. The median disease disease duration before RTX treatment was 5 years. Previous treatments of these 25 patients included corticosteroids, hydroxychloquine, methotrexate, I.V. cyclophosphamide, and 2 patients received intravenous immunoglobulin therapy. Nine patients were treated repeatedly with RTX during the follow-up period. The overall response rate to RTX treatment was 80% (a complete response in 72% and a partial response in 8%). RTX was used as a maintenance therapy in 2 patients. Relapses occurred in 6 patients after a median of 171 months (range: 1-60 months) following the initial treatment with RTX. Mild-to-moderate infusion reactions were seen in 2 patients but no serious infections were recorded. One patient died due to a massive cerebrovascular accident, 1 developed oral cancer, 1 developed end-stage renal failure, 1 had worsening of her skin rashes and finally proteinuria worsened in another patient.
Conclusions. RTX can be considered as an off-label still effective alternative therapeutic approach for patients with SLE developing manifestations refractory to conventional immunosuppressive treatments. For most patients, RTX was safe and well tolerated.

Key words: rituximab, efficacy, systemic lupus erythematosus

S3: Microparticles and biomarkers in lupus nephritis

S3:03

ENDOTHELIAL PROGENITOR CELLS AND ENDOTHELIAL MICROPARTICLES IN ANTIPHOSPHOLIPID SYNDROME: A NEW PARADIGM OF ENDOTHELIAL DAMAGE

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Objective. Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by recurrent thromboembolic events and pregnancy morbidity associated to the presence of specific serum antibodies directed towards membrane proteins binder phospholipids (aPL). Endothelial dysfunction represents the earlier and reversible stage of subclinical atherosclerosis that characterizes these patients. An altered profile of endothelial progenitor cells (EPCs) and endothelial microparticles (EMPs) could promote endothelial damage. Few studies suggested that EMP release is stimulated by circulating aPL. A small study previously investigated EPC number in 7 APS patients showing no difference compared to healthy subjects. Our aim was to evaluate the levels of circulating EPCs and EMPs in primary APS.
Design and Method. Consecutive patients with primary APS (PAPS) attending the Lupus Clinic of Sapienza Univeristy of Rome as well age- and sex-matched controls were recruited.After a written informed consent was obtained, a fasting blood sample was collected to analyze circulating EPCs and serum EMPs. Purified EPCs (CD34+/KDR+) and EMPs (CD31+/CD41a-) were quantified by flow cytometry analysis.
Results. We enrolled 11 PAPS patients (mean age 44±12 years) with previous thromboembolic events and 12 healthy controls.Compared to heathly subjects, PAPS patients showed a lower EPC percentage (mean±standard deviation 0,004±0,003 vs 0.001±0,00 respectively; p=0.0002) and a higher EMP number [median(IQR) 18(12.5) vs 63 (62.7), respectively; p=0.0001].
Conclusions. EMPs seems to have a pro-trhombotic effect and may contribute to development ot thrombotic events; besides, EMPs are known to activate and damage endothelial cells by increasing the expression of inflammatory cytokines and adhesion molecules and by up-regulating the inducible nitric oxide synthase; thus, EMPs may be associated to to the atherosclerotic process.
The results of this study suggest that endothelial cells activated by circulating aPL may result in the release of EMPs that, in turn, can perpetuate the endothelial damage. Moreover, our cohort of APS patients has a reduced number of circulating EPC that could contribute to the impairment of endothelial repair and the progression of atherosclerosis.

Key words: endothelial progenitor cells, endothelial microparticles, antibodies anti phospholipids

S3:04

THE ROLE OF OSTEOPONTIN AS A CANDIDATE BIOMARKER OF RENAL INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

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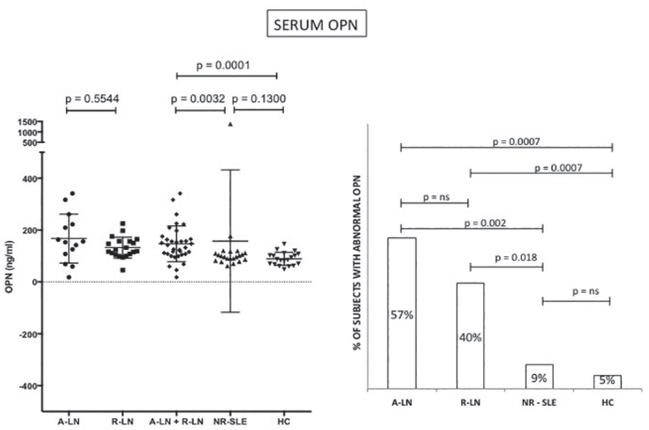
Objective. Kidney biopsy is still the gold standard procedure for the diagnosis of Lupus Nephritis (LN), one of the most severe manifestations of Systemic Lupus Erythematosus (SLE). Conventional biomarkers of disease activity or renal function, such has complementemia, anti-dsDNA, serum creatinin, urinary sediment and proteinuria, do not have a sensitive diagnostic and prognostic value, therefore new biomarkers are needed to help predicting LN development or monitoring disease activity. Osteopontin (OPN) is a pro-inflammatory molecule able to stimulate the immune system and it has been detected in renal tissue. The aim of this study was to evaluate OPN as a candidate biomarker of renal involvement in SLE patients and correlate it with disease activity indices and laboratory features.
Design and Method. OPN was measured in serum and urine of SLE patients with active LN (n=14), LN in remission (n=20), SLE without kidney involvement (n=22) and age and sex-matched healthy controls (n=20).
Results. OPN levels were significantly higher in urine than in serum in both patients and controls (p<0.001). Serum OPN levels were higher in LN patients

[median (interquartile range)] [73.06 (34.87)] than in controls [58.12 (21.26)] and in SLE patients without renal involvement [53.39 (15.79)] (p<0.0001 and 0.0032 respectively), regardless the phase of renal activity (p=0.2555) (Figure). SLE patients without renal involvement and controls showed similar serum levels (p=0.1300). We detected a direct correlation between hypocomplementemia and OPN serum levels in patients with LN (p=0.014; R=0.438). Moreover, a higher percentage of patients with LN, compared to SLE without LN and controls, showed abnormal serum OPN (levels exceeding the 97th percentile of controls value) (Figure).



-LN= Active Lupus Nephritis, R-LN = Remission Lupus Nephritis, NR-SLE = Non Renal Systemic Lupus Erythematosus, HC = Healthy Controls

Conclusions: Our data suggest that serum OPN could be considered as a possible biomarker of renal involvement, but without the ability to differentiate between active and remission LN.

Key words: lupus nephritis, biomarker, osteopontin

S3:05

BIOMARKERS IN LUPUS NEPHRITIS: POSSIBLE ROLE OF SERUM CYSTATIN-C, SERUM BETA2- MICROGLOBULIN, URINARY ALPHA1 - MICROGLOBULIN AND ALBUMIN/CREATININ RATIO (ACR)

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Objective. Lupus nephritis is one of the most severe manifestations of Systemic Lupus Erythematosus (SLE), that is able to influence the prognosis of lupus disease and treatment decisions. A correct diagnosis is mandatory as early as possible, not only at the onset but also during disease exacerbations.
The purpose of the study is to identify possible new biomarkers more sensitive than conventional ones (complement, antiDNA antibodies, 24 hours proteinuria and serum creatinine) for diagnosis and monitoring of lupus nephritis.
Design and Method. Seventy-three consecutive SLE nephritis patients were enrolled on the basis of the renal involvement and divided in active and inactive nephritis. Demographic, clinical and laboratory data were collected at different time-points: at baseline (T0), after three (T3) and after six (T6) months. All the samples were assayed for serum levels of cystatin C and urinary levels of alpha1-microglobulin, using immuno-turbidimetric test, serum beta2-microglobulin by nephelometric test, and albumin/creatinin ratio (ACR) was determined.
Results. Of the 73 enrolled patients with lupus nephritis (83% females, mean age of 38.5±12.0 years, disease duration of 13.0±8.8 years), at baseline 24 (32.8%) had active nephritis and 49 (68.2%) had inactive nephritis. Patients with active nephritis had higher levels of SLEDAI (p<0.01), 24 hours proteinuria (p<0.01), as well as serum cystatin C (p=0.01), urinary alpha1-microglobulin (p=0.005) and ACR (p<0.01). Eleven (22.4%) of 49 patients with inactive nephritis at baseline, had a renal flare during the follow up. At baseline these patients had higher values of serum cystatin C (1.9±0.6 vs 0.9±0.2 mg/l, p=0.001), serum beta2-microglobulin (4.0±2.6 vs 2.0±0.8 mg/dl, p=0.001), urinary alpha1-microglobulin (p<0.01) and ACR (279.9±6.9 vs 440.1±12.0 mg/g, p<0.01) than patients with persistent inactive nephritis during the follow up. There were no differences in the conventional biomarkers used in the monitoring of nephritis between relapsing and no relapsing SLE nephritis patients.
Conclusions: The results of this study, although preliminary, suggest that these new possible biomarkers, integrated with conventional biomarkers, can give additional information on the state of nephritis and can also predict earlier nephritic flares.

Key words: lupus nephritis, biomarkers, cystatin c and a1microglobulin

S3:06

THE ROLE OF INNATE IMMUNITY IN THE PATHOGENESIS OF LUPUS NEPHRITIS: FOCUS ON INTERLEUKIN 32

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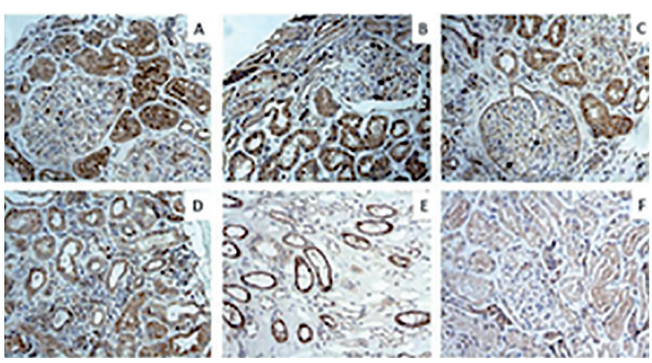
Objective. Lupus nephritis (LN) is one of the most severe features of systemic lupus erythematosus (SLE) involving an increase in morbidity and mortality rates. Cytokines and chemokines are secreted locally in the earlier phases of glomerular inflammation and play a key role in the further development of kidney infiltrates leading to the clinical manifestation. Interleukin 32 (IL32) is a newly described cytokine that exhibits several properties typical of proinflammatory cytokines. In particular, IL32 induces the production of different proinflammatory cytokines, the maturation and activation of dendritic cells, resulting in Th1 and Th17 polarization, and endothelial activation. To investigate serum and urinary levels of IL32 in a cohort of LN patients compared to SLE patients without renal involvement and healthy controls (HC). Further aims were to investigate kidney expression of IL32 in different histological classes of LN.



Design and Method. Serum and urinary IL32 concentrations were measured using ELISA; for the evaluation of the expression of IL32 in renal biopsies we used a polyclonal rabbit anti-human IL32.
Results. We recruited 60 LN patients, 50 SLE patients without renal involvement and 30 HC; 40 LN patients had an active disease (a-LN) and the remaining 20 were in remission (r-LN). IL32 serum levels were significantly higher in patients with r-LN (median 1368, IQR 3910) and HC (median 721, IQR 2271) compared to SLE patients without renal involvement (median 203, IQR 662.8 pg/ml) (p=0.03 and p=0.018, respectively). There were no significant differences in urinary IL32 between LN patients, SLE patients without renal involvement and HC. In LN patients, we observed a direct correlation between IL32 serum levels and disease duration (p=0.02; r 0.2978). Immunohistochemical analysis performed on renal biopsies of 20 a-LN and 8 HC showed that IL32 was strongly expressed in renal samples of LN patients, especially in patients with IV LN, compared to controls.
Conclusions. Data from this study show increased serum levels of IL32 in patients with remission phase of LN in comparison to SLE patients without renal involvement as well as an increase in the expression of this cytokine in renal tissues of patients with active LN. Increased expression of IL32 in renal tissue of patients with active LN could suggest local production of IL32 and its role in the pathogenesis of LN.

Key words: systemic lupus erythematosus, lupus nephritis, interleukin 32

S4: Targeted therapy in SLE

S4:03

ANTI-PENTRAXIN3 (PTX3) ANTIBODIES ARISING FOLLOWING IMMUNIZATION WITH PTX3 IMPROVE SURVIVAL AND DELAY LUPUS-LIKE GLOMERULONEPHRITIS IN NZB/NZWF1 MICE

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Objective. Lupus glomerulonephritis (LGN) is one of the most threatening manifestations of systemic lupus erythematosus (SLE). We had demonstrated a negative association between high levels of anti-pentraxin 3 (PTX3) antibodies and LGN in humans. The current experiment was aimed at investigating the protective role of anti-PTX3 in a murine model of lupus-like nephritis and inherent mechanisms of action of anti-PTX3 antibodies.
Design and Method. 30 New Zealand Black/White (NZB/NZW F1) mice were subdivided into 3 groups of 10 mice each and injected with 100 µg of PTX3 in 100 µl of alum and 100 µl of phosphate buffer saline (PBS) (group 1), 100 µl of alum and 100 µl of PBS (group 2) or 200 µl of PBS alone (group 3), 3 times 3 weeks apart, from week 11 to week 17. They were followed until natural death. Levels and time of occurrence of anti-PTX3, anti-dsDNA and anti-C1q antibodies were evaluated by monthly blood sampling, and proteinuria by weekly urine sampling. Survival and proteinuria-free survival (proteinuria <300mg/dl) were evaluated according to Kaplan-Meier method. Harvested kidneys from all groups underwent histological analysis and immunohistochemistry. We explored the effect of anti-PTX3 antibodies on C1q binding to immobilized PTX3-anti-PTX3 immunecomplexes *in vitro* using human SLE sera. Qualitative characterization of human IgG anti-PTX3 was performed.
Results. Only group 1 mice developed anti-PTX3 antibodies. Anti-dsDNA and anti-C1q antibodies appeared significantly later and at lower levels in group 1 mice ($p<0.0001$). Group 1 mice lived significantly longer than control mice ($p=0.03$) and had their proteinuria significantly delayed and reduced ($p<0.05$). Histopathological analyses confirmed minor kidney injury in group 1 mice despite an average older age. PTX3 immunostaining was increased in glomerula and tubuli of mice not immunized with PTX3. Incubation of human SLE sera positive for anti-PTX3 antibodies with C1q and fixed PTX3 decreased C1q binding to PTX3-anti-PTX3 immunecomplexes. Qualitative characterization of human IgG anti-PTX3 showed an increased proportion of IgG4.
Conclusions. Following immunization with PTX3, anti-PTX3 antibodies arise which are likely to delay lupus-like nephritis and prolong survival of NZB/NZW F1 mice. *In vitro* observations suggest anti-PTX3 antibodies may interfere with C1q fixation and complement activation

Key words: anti-PTX3, complement, lupus nephritis

S4:04

IL-2 THERAPY REDUCES INTRARENAL TCON HYPERACTIVITY AND RENAL INFLAMMATION IN NZB/W MICE WITH ACTIVE LUPUS NEPHRITIS

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Objective. An acquired deficiency of interleukin-2 (IL-2) and related defects in regulatory T cell (Treg) biology contribute to the pathogenesis of systemic lupus erythematosus (SLE) (Humrich *et al*. 2010, von Spee-Mayer *et al*. 2015). Kidney-infiltrating $CD4^+$ T cells play a crucial role in the progression of lupus nephritis (LN). However, the role of kidney-infiltrating Treg in the pathogenesis of LN is poorly understood. The aim of this study was to investigate whether an IL-2 deficiency is also present in the inflamed kidney and whether this affects intrarenal Treg thereby contributing to renal inflammation. Furthermore we investigated whether and how intrarenal Treg and renal inflammation can be influenced by IL-2 therapy.
Design and Method. Intrarenal $CD4^+$ T cells and the *in vitro* IL-2 production of intrarenal $CD4^+CD44^+$ T cells of (NZBxNZW) F1 mice (NZB/W) with different disease activities were analyzed by flow cytometry. NZB/W mice with active LN were treated subcutaneously with recombinant mouse IL-2 for a total of 29 days. Kidneys were scored at a histological level using the renal activity index (AI) and changes in intrarenal $CD4^+$ T cells were assessed at different time points during the IL-2 treatment.
Results. Intrarenal Treg exhibit characteristic signs of IL-2 deprivation, including low expression of CD25, in parallel to a progressive hyperactivity of intrarenal Tcon. These Treg defects were associated with a diminished production of IL-2 and an increased production of IFNγ by kidney-infiltrating Tcon. IL-2 treatment increased the frequency of intrarenal $CD25^+$Helios+Treg, strongly reduced the hyperactivity of intrarenal Tcon and resulted in a clinical and histological amelioration of LN.
Conclusions. Our data indicate that on the one hand an IL-2 deficiency is present in the inflamed kidney, thereby contributing to renal inflammation. On the other hand, long-term IL-2 treatment is able to reduce intrarenal Tcon hyperactivity and to diminish kidney inflammation in NZB/W mice. This shows the close relation between intrarenal IL-2 deficiency and defects of intrarenal Treg, the hyperactivity of intrarenal Tcon and the severity of LN. This and the reversibility of these immune pathologies by IL-2 treatments provide additional rationales for an IL-2 based immunotherapy of human SLE and in particular of LN.

Key words: treg, IL-2, lupus nephritis

S4:05

SURVIVAL RATE AND CAUSES OF WITHDRAWAL OF BELIMUMAB IN SLE IN A REAL LIFE SETTING

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Objective. Systemic Lupus Erythematosus (SLE) is a chronic disease requiring long-term treatment. Even though immunosuppressive therapy improved the survival, a great percentage of SLE patients exhibit a persistently active disease or disease flares. Belimumab (BLM), an anti-B Lymphocyte Stimulator (BLyS), is the only biological drug approved for the treatment of active SLE patients not responding to standard of care, without active kidney or neuropsychiatric involvement.
Aim of the study was to analyse 24 months survival of BLM treatment and causes of withdrawal in a monocentric cohort of SLE patients followed-up in a daily practice setting.

Table I. SLEDAI 2K, C3 and C4, prednisone dose and anti-dsDNA status during the follow-up.

	T0	T3	T6	T12	T24
N of patients	20	19	11	10	3
PDN mg/sett (#)	70 (39.4)	37.5 (35)	35 (22.5)*	30 (19)**	27.5 (12.3)
SLEDAI 2K (#)	6 (4)	6 (2)	4 (3.5)	2 (6)≠	1.5 (1)
C3 (#)	70 (21.5)	70 (23)	63 (20)	68.5 (7.8)	90 (28)
C4 (#)	13 (6)	14 (6)	8 (5)	10 (7.5)	14 (4.5)
aDNA+ (%)	100	10	20	5	33

(#) median (interquartile range); *$p=0.06$; **$p=0.01$; a$p=0.002$; ≠$p<0.05$.

Table I summarizes the trend of SLEDAI 2K, C3 and C4, prednisone dose and percentage of patients positive for anti-dsDNA during the follow-up. Mean BLM treatment duration was 9.9±8.07 months. Ten out of the 20 patients reached 12 months of observation and only 15% the 24 months. In 3 out of 20 patients (15%) adverse events were the cause of BLM withdrawal (severe infection in one patient, severe bradychardia in one and infusion reaction in another one). In 5 patients (25%) BLM was discontinued for lack/loss of efficacy on articular and skin manifestations, after a mean follow-up of 9.5 months; one patient developed a severe neuropsychiatric flare after the second BLM infusion and was admitted in our hospital for depression and suicidal thoughts;one other patient lost to follow-up and two patients withdrew BLM therapy to plan a pregnancy.
Design and Method. The study was proposed to all the patients who started BLM. After the informed consent was obtained, demographic, clinical and serological data, indication to BLM and concomitant therapies were registered. At baseline and after 3, 6, 12 and 24 months of follow-up, disease activity (SLE Disease Activity Index – SLADAI 2K), C3 and C4 levels, anti-dsDNA status and weekly dose of glucocorticoids were recorded. After 3, 6,12 and 24 months, differences in SLEDAI 2K, C3 and C4 and prednisone-equivalent dose com-

pared to baseline were evaluated by Wilcoxon test. P value <0.05 was considered significant

Results. We enrolled 20 Caucasian females with mean age of 42.5±9.66 years and mean disease duration of 19.5±10.24 years. Indications for starting BLM were: mucocutaneous involvement (n=6, 30%), arthritis (n=14, 70%), lung involvement (1 patient, 5%). At baseline, all the patients were taking prednisone; in addition, 60% were taking hydroxychloroquine, 30% mycophenolate mofetil, 15% azathioprine, 20% cyclosporine, 15% methotrexate and 5% thalidomide.

Conclusions. In our monocentric cohort of SLE patients treated in a real life setting, BLM showed good safety profile; the cause of withdrawal was lack of efficacy or disease flare in up to one third of patients; patients continuing BLM showed a significant decrease of weekly glucocorticoid dose starting from the 6th month and a SLEDAI 2k decrease from the 12th month of follow-up.

Key words: SLE, belimumab, biologic

S4:06

THERAPEUTIC APPLICATION OF HUMAN UMBILICAL CORD WHARTON JELLY-DERIVED MESENCHYMAL STEM CELLS (HUCMS) IN SYSTEMIC LUPUS ERYTHEMATOSUS: PITFALLS AND PERSPECTIVES

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Objective. hUCMS are adult stem cells displaying immune-modulatory properties *in vitro* on effector immune cells isolated from normal subjects and patients with rheumatoid arthritis. This effect is exerted either by contact or through the secretion of soluble mediators. However, we previously demonstrated that effector immune cells of patients with primary Sjögren's syndrome (pSS) and type 1 diabetes (T1D) inhibit hUCMS by contact thereby hampering their immune-modulatory properties *in vitro*. To overcome such effect, we recently developed an endotoxin-free alginate matrix, which can be used to microencapsulate (CpS) different cell types and graft them into a non-immunosuppressed host. CpS-hUCMS are able to inhibit pSS and T1D PBMC cell proliferation and to rebalance the T-effector/T-regulatory (reg) cell ratio via the conversion of Th17 cells into Treg cells *in vitro*. Of interest, these effects are inversely correlated to hUCMS number (Alunno A, Montanucci P *et al*. Rheumatology (Oxford) 2015, Montanucci P, Alunno A *et al*., Clin Immunol 2016). Aim of this study was to verify the *in vitro* effect of such CpS-hUCMS system on effector cells from systemic lupus erythematosus (SLE) patients.

Design and Method. Ten SLE patients and 5 healthy donors (HD) were enrolled. Co-cultures of either free or IFN-gamma triggered CpS-hUCMS plus PBMCs were arranged at different ratios. Lymphocyte proliferation was assessed by CFSE dilution. Phenotypic analysis of PBMCs by flow cytometry and of hUCMS by PCR was performed after culture.

Results. Free hUCMS failed to suppress SLE T cell proliferation, similarly to pSS and T1D. Surprisingly, however, also CpS-hUCMS failed to inhibit SLE PBMC cell proliferation at any ratio tested. In fact, CpS-hUCMS did not reduce Th1 and Th17 cell percentage and did not modulate FoxP3 expression in Treg cells. CpS-hUCMS harvested after culture with SLE PBMCs, displayed the same gene expression profile as those cultured with pSS and T1D allowing to rule out any inhibition by SLE effector cells.

Conclusions. This is the first study evaluating the effects of hUCMS on T cells in SLE employing a new technology of drug delivery that may be applied *in vivo*. CpS-hUCMS appear unable to inhibit SLE pathogenic T cells and to foster the regulatory counterpart. However, this appears not to be linked to hUCMS inhibition by SLE effector cells. These intriguing results appears to be in line with our previous data showing a certain resistance of SLE effector T cells to immune-modulatory stimuli, like those from self Treg cells (Nocentini G, Alunno A et al, Arthritis Res Ther 2014). Although we are currently performing additional experiments employing higher hUCMS/PBMC ratios to verify the possibility to bypass SLE effector cell resistance, these data open possible interesting scenarios of research aimed to unmask causes and mechanisms at the basis of effector T cell resistance in SLE.

Key words: mesenchymal stem cells, Th17 cells, treg cells

S5: Redefining lupus

S5:03

LUPUS IN THE COMMUNITY VERSUS REFERRAL CENTRES: DISEASE PHENOTYPE AND SEVERITY AND IMPLICATIONS FOR CLINICAL CARE AND RHEUMATOLOGY TRAINING

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Objective. Systemic lupus erythematosus (SLE) is a heterogeneous disease with most reports originating from tertiary referral centres, which carries the potential of referral bias for the most severe forms of the disease. We sought to quantitate the differences in disease phenotype and severity between lupus in the community versus the disease seen in major centres.

Table I. Clinical and serologic characteristics and severity of disease in the two cohorts.

	"Leto" population-based cohort (828 patients)	"Attikon" cohort (150 patients)	
Age at diagnosis, mean (SD)	43.0 (15)	38.7 (16)	
Female : Male	13:1	12.6:1	
Manifestation, n (%)			*p-value*
• Photosensitivity	703 (85)	80 (55)	**<0.0001**
• Malar rash	480 (58)	58 (39)	**<0.0001**
• Discoid rash	99 (12)	10 (7)	0.61
• Mucosal ulcers	394 (48)	31 (21)	**<0.0001**
• Arthritis	753 (91)	119 (80)	**0.0012**
• Serositis	124 (15)	31 (21)	0.086
• Nephritis	104 (13)	25 (17)	0.149
• Neuropsychiatric	67 (8)	30 (20)	**<0.0001**
• Haematological	248 (30)	56 (38)	0.067
• Low C3/C4	176 (21)	61 (51*)	**<0.0001**
• Anti-dsDNA (+)	190 (23)	50 (38*)	**0.0003**
• aPL (+)	118 (14)	25 (29*)	**0.0008**
Disease severity, n(%)			
• Mild	414 (50)	49 (33)	
• Moderate	273 (33)	56 (37)	**<0.0001****
• Severe	141 (17)	45 (30)	

* In patients where these tests are currently available;
** For mild vs. moderate/severe disease.

Design and Method. The Rheumatology and Clinical Immunology unit of "Attikon" University hospital, Athens, was used as a tertiary referral centre. Data from 150 SLE patients registered to date were collected for disease manifestations, number of ACR or SLICC criteria and treatments received. In parallel, data from the population-based SLE registry "Leto" in Crete (total 828 patients) were used as a comparator. Disease was categorized as severe, moderate, or mild, based on the presence of British Isles Lupus Assessment Group (BILAG) group A (severe), B (moderate) or C/D/E (mild) manifestations at any time during the course of the disease.

Results. The "Attikon" referral centre cohort included more patients with major organ involvement, especially primary neuropsychiatric disease (20% vs. 8%, $p<0.0001$). Conversely, SLE patients from the "Leto" population-based registry displayed significantly more frequently cutaneous, mucosal and musculoskeletal manifestations (Table I). Serologic abnormalities were more prevalent in the "Attikon" cohort, as indicated by the increased proportion of patients with low complement and high ant-dsDNA levels. Categorization of disease phenotype according to BILAG manifestations revealed significantly more patients in the moderate/severe group in the "Attikon" cohort (67% vs. 50% in the "Leto" cohort, $p<0.0001$).

Conclusions. This is the first report quantifying clinical differences between lupus in the community versus tertiary referral centres, with obvious implications for patient care and training of rheumatology fellows, who need to recognize milder cases of the disease.

Key words: epidemiology, disease severity, lupus nephritis

S5:04

MULTIPARAMETRIC DETECTION OF AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ENABLES DEFINITION OF SLE PATIENT SUBGROUPS

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Objective. Systemic lupus erythematosus (SLE) is a heterogeneous disease with respect to disease manifestations, disease progression and treatment response. Therefore, strategies to identify biomarkers that help distinguishing SLE subgroups are a major focus of biomarker research. Current diagnostic methods for determining autoantibodies in SLE have mainly focused on a relatively small set of autoantibody targets and fall short to exploit the great number of available autoantibody targets in SLE. We reasoned that a multiparametric autoantibody profiling approach combined with data mining tools could be applied to identify SLE patient clusters.
Design and Method. A total of 86 antigens were selected for this study of which 50 antigens have been previously associated with SLE and 36 were recently identified by us in large-scale autoantibody screening studies. The selected antigens can be grouped into different functional protein families (*i.e.* DNA-binding, RNA-binding and cytoskeletal proteins) or belong to immune-relevant biological pathways. The array was applied to analyze the autoantibody reactivity profiles of 69 SLE patients and 59 healthy controls (HC).
Results. Sixty-four autoantibodies were significantly ($p<0.05$) increased in SLE compared to HC. Using binary cut-off thresholds (95% quantile of HC), hierarchical clustering of SLE patients yields five clusters, which differ qualitatively and in their total number of autoantibodies. Two patient subgroups showed the highest number of overall accumulated autoantibody reactivity (31% and 48% all tested antigens) and were more frequently diagnosed to have glomerulonephritis (GLMN) compared to other clusters. The two clusters can be distinguished by characteristic cluster-driving autoantibody reactivities to neutrophilic granule (ANCA) and anti-dsDNA, anti-Sm and anti-ribosomal P reactivities, respectively. In addition, groups of autoantibodies directed against distinct intracellular compartments and/or biological motifs characterize the different SLE subgroups.
Conclusions. Although the autoantibody repertoire in SLE appears to be highly diverse, our multiplexing approach of 86 antigens enabled us to display common, overlapping and distinct autoantibody reactivity signatures in SLE patients. Validation studies of the identified landmark antigens driving cluster formation will provide evidence whether they will support the distinguishing of basic patient cohorts and can be matched to differences in the SLE etiology, enabling them to be utilized in personalized medicine approaches.

Key words: autoantibody, patients subgrouping, nephritis

S5:05

COMPARISON OF BRITISH ISLES LUPUS ASSESMENT GROUP (BILAG) -2004 AND CLASSIC BILAG INDICES

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Objective. BILAG devised a transitional index for measuring disease activity in lupus patients based on the principle of the physician's intention to treat, in which items that are present over the last 4 weeks are recorded as new, worse, the same or improving. A categorical score is calculated for each system based on how the items are recorded and an A score reflects most severe disease activity requiring intense immunosuppression, B score reflects disease activity requiring lesser amounts immunosuppression, C score reflects mild disease requiring symptomatic therapy, and a D or E score reflects no disease activity or no involvement respectively. It became clear that the version of classic BILAG index contained items due to damage, certain phenotypes and conditions not related to lupus, suboptimal scoring for renal and haematology system and the difficulty to score the cardiorespiratory, gastro-intestinal and ophthalmic systems. The BILAG-2004 index was devised to correct the above and other problems with the classic BILAG index. The final version of BILAG-2004 index consists of 97 items, distributed between 9 systems and has 7 systems in common with the classic BILAG; the glossary definition and scoring of the component items are different, however the fundamental concept of the physician's intention to treat remained the same. The aim of this observational study was to compare data collected at the same time on the same patients for the assessments of lupus disease activity using classic BILAG index and the final version of the BILAG 2004 index in the validation of the BILAG 2004 index
Design and Method. Dataset from BILAG-2004 validation longitudinal study used. Descriptive analysis of all BILAG 2004 and classic BILAG A and B scores. Descriptive analysis on observations with BILAG-2004 score A or B but without Classic BILAG A or B Descriptive analysis on observations with Classic BILAG score A or B but without BILAG-2004 A or B Comparison of all numerical scores for these observations with classic BILAG and BILAG 2004 indices.
Results. see tables

1) Baseline data

• There were 1767 observations (assessments) in 353 patients in the longitudinal study in total. The median duration of follow-up was 11 months (range 1–26) and median number of assessments per patient was four (range 2–18).

• There were 554 observations (in 204 patients) with 1 or more BILAG-2004 Grade A or B scores

System	BILAG-2004 Grade A	BILAG-2004 Grade B	Total BILAG grade A or B
Constitutional	4	20	24
Mucocutaneous	32	251	283
Neuropsychiatric	13	14	27
Musculoskeletal	38	150	188
Cardiorespiratory	6	62	68
GIT	0	7	7
Ophthalmic	2	8	10
Renal	31	84	115
Haematological	0	6	6

• There were 626 observations (in 225 patients) with 1 or more Classic BILAG Grade A or B scores

System	Classic BILAG Grade A	Classic BILAG Grade B	Total Classic grade A or B
Constitutional	6	53	59
Mucocutaneous	24	202	226
Neuropsychiatric	17	15	32
Musculoskeletal	52	188	240
Cardiorespiratory	1	22	23
Vasculitis	8	39	47
Renal	15	70	85
Haematological	7	193	200

Note: The sum of the total column could exceed the number of observations as some observations (assessments) have more than 1 A or B score

2) Comparison of BILAG 2004 and classic BILAG A and B scores

Note: The sum of the total column could exceed the number of observations as some observations (assessments) have more than 1 A or B score

Table 1: Comparison of number and percentages of observations with BILAG-2004 A or B scores and Classic A or B scores by systems (1767 total observations).

System	BILAG-2004 Grade A or B	%Total observations	Classic Grade A or B	%Total observations
Constitutional	24	01.5%	59	03.3%
Mucocutaneous	283	16.0%	226	12.7%
Neuropsychiatric	27	01.5%	32	01.8%
Musculoskeletal	188	10.6%	240	13.5%
Cardiorespiratory	68	03.8%	23	01.3%
GIT	7	00.4%	Vasculitis 47	Vasculitis 02.7%
Ophthalmic	10	00.6%	-	-
Renal	115	06.5%	85	04.8%
Haematological	6	00.3%	200	11.3%

Table 2: Comparison of number and percentages of observations with BILAG 2004 or classic BILAG A scores by system (out of 1767 total observations)

System	BILAG-2004 Grade A	%Total observations	Classic Grade A	%Total observations
Constitutional	4	00.2%	6	00.3%
Mucocutaneous	32	01.8%	24	01.4%
Neuropsychiatric	13	00.7%	17	01.0%
Musculoskeletal	38	02.1%	52	02.9%
Cardiorespiratory	6	00.3%	1	00.1%
GIT	0	0	Vasculitis 8	Vasculitis 00.5%
Ophthalmic	2	00.1%	-	-
Renal	31	01.7%	15	00.8%
Haematological	0	0	7	00.4%

Table 3: Comparison of number and percentages of observations with BILAG 2004 or classic BILAG B scores by system (out of 1767 total observations)

System	BILAG-2004 Grade B	%Total observations	Classic Grade B	%Total observations
Constitutional	20	01.1%	53	03.0%
Mucocutaneous	251	14.2%	202	11.4%
Neuropsychiatric	14	00.7%	15	00.8%
Musculoskeletal	150	08.4%	188	10.6%
Cardiorespiratory	62	03.5%	22	01.2%
GIT	7	00.4%	Vasculitis 39	Vasculitis 02.2%
Ophthalmic	8	00.5%	-	-
Renal	84	04.7%	70	04.0%
Haematological	6	00.3%	193	10.9%

Table 4: Number (and percentage) of observations with BILAG-2004 Grade A or B score but without Classic BILAG Grade A or B scores (as a percentage of observations with the relevant BILAG 2004 system score)

• The following were observed in only 64 assessments in 35 patients out of 1767 total observations (assessments)

System	BILAG 2004 total A	BILAG 2004 A not classic A or B	BILAG 2004 total B	BILAG 2004 B not classic A or B	BILAG 2004 total A or B	BILAG 2004 A or B not classic A or B
Constitutional	4	0	20	0	24	0
Mucocutaneous	32	0	251	13 (5.2%)	283	13 (4.5%)
Neuropsychiatric	13	2 (15.3%)	14	1 (7.1%)	27	3 (11.1%)
Musculoskeletal	38	0	150	9 (6.0%)	188	9 (4.5%)
Cardiorespiratory	6	0	62	13 (20.9%)	68	13 (19.1%)
GIT	0	0	7	4 (57.1%)	7	4 (57.1%)
Ophthalmic	2	1 (50%)	8	3 (37.5%)	10	4 (40.0%)
Renal	31	1 (3.2%	84	21 (25%)	115	22 (19.1%)
Haematological	0	0	6	0	6	0

3) Number (and percentage) of observations with Classic BILAG Grade A or B scores but without BILAG-2004 Grade A or B scores (as a percentage of observations with the relevant classic BILAG system score)

• The following were observed in only 136 assessments in 88 patients out of 1767 total observations (assessments)

System	Classic total A	Classic not 2004 A or B	Classic total B	Classic not 2004 A or B	Classic total A or B	Classic not 2004 A or B
Constitutional	6	0	53	11 (20.7%)	59	11 (18.6%)
Mucocutaneous	24	0	202	4 (1.9%)	226	4 (1.7%)
Neuropsychiatric	17	1 (5.8%)	15	4 (16.6%)	32	5 (15.6%)
Musculoskeletal	52	0	188	43 (22.8%)	240	43 (17.9%)
Cardiorespiratory	1	0	22	0	23	0
Vasculitis	8	1 (12.5%)	39	2 (5.1%)	47	3 (6.3%)
Renal	15	0	70	8 (11.4%)	85	8 (9.4%)
Haematological	7	0	193	72 (37.3%)	200	72 (36.0%)

Conclusions. The BILAG 2004 index is more relevant to lupus disease assessment and reflects treatment changes made in practice better. Although comparison between the BILAG with the classic BILAG can be made it is not possible to calculate an appropriate mathematical conversion from one to the other due to the natures of the differences. Both indices are best used as intended as categorical scores for each system, but when a total numerical score is needed, an appropriate method has been published for each index and is appropriate for comparing patients assessed by the same index. When comparing studies using different indices, it would be best to compare the results of assessments using categorical data not numerical data.

Key words: BILAG-2004, classic BILAG

S5:06

MULTIPLE AUTOIMMUNE SYNDROME DOES NOT PROTECT FROM SEVERE ORGAN INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS – 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 clinical and immunological differences. 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 MAS with SLE would protect from severe organ involvement in SLE alone, based on clinical, immunological and genetic data.

Design and Method. Adult SLE 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 medical files. 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. 232 SLE patients were studied (91.8% women, 8.2% men). 67.1% had only SLE (monoautoimmunity subgroup) and 32.9% had SLE plus 2 or more other AIDs (MAS subgroup). The mean age at SLE diagnosis was 31.76 yo and mean follow-up time of 15.47 years. NPSLE (OR=3.15, 95%IC[1.64-6.05]) due to focal involvement (OR=2.49, 95%IC[1.22-5.07]), mucocutaneous subacute SLE (OR=2.69, 95%IC[1.16-6.28]), musculotendinous involvement (OR=2.05, 95%IC[1.00-4.21]), haematological involvement (OR=2.74, 95%IC[1.21-6.24]) and Raynaud's phenomenon (OR=2.88, 95%IC[1.59-5.22]) were more prevalent in the MAS subgroup.

After elimination of confounding factors, only anti-U1RNP and anti-CCP antibodies were positively associated with MAS. No other involvement had a significantly different association between subgroups.

In our study sample, HLA-DRB1*03 was more frequent than in the general population. HLA-DRB1*07 frequency was significantly higher in the mono subgroup (OR=0.24, 95%IC[0.09-0.65]). We found no other differences between the mono and MAS subgroups.

In the MAS subgroup, HLA-DRB1*15 was significantly less frequent in the patients with focal NPSLE (Chi2=5.55, p=0.022); HLA-DRB1*4 was significantly less frequent in the patients with muscular and tendinous involvement (Chi2=4.60, p=0.045); HLA-DRB1*11 was significantly less frequent in the patients with haematological involvement (OR=0.06, 95%IC[0.004-0.762]).

No statistically significant differences in PTPN22 frequencies were observed between the subgroups.

Conclusions. Against expectations, MAS patients seem to have a more serious disease course (NPSLE, haematological, mucocutaneous subacute) than mono SLEs. Raynaud's phenomenon occurred proportionaly more in MAS, probably due to its transversality in AIDs. Could anti-U1RNP antibody represent a subgroup of patients that are evolving towards MCTD or could it represent an uncovered risk to MAS? HLA-DRB1 frequencies in the study population confirmed previous studies that associated HLA-DRB1*03 with an increased susceptibility to SLE. The possible protective effect of HLA-DRB1*04, HLA-DRB1*11 and HLA-DRB1*15 of specific involvements in MAS must be confirmed in larger cohorts. The increased frequency of HLA-DRB1*07 in the mono subgroup might signal this allele as a possible protector against susceptibility to poly or multi autoimmunity in SLE patients.

Key words: multiple autoimmune syndrome, systemic lupus erythematosus, genetic risk factors

S6: B cells and plasma cells in lupus nephritis

S6:03

A UNIQUE B CELL PHENOTYPE IDENTIFIED IN AFRICAN AMERICAN LUPUS PATIENTS

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Objective. Systemic Lupus Erythematosus (SLE) is a complex systemic autoimmune disease driven by both innate and adaptive immune cells. African Americans tend to present with more severe disease at an earlier age compared to patients of European ancestry. Our purpose was to better understand the immunological differences between African American and European American patients.
Design and Method. We analyzed by flow cytometry the frequencies of B cell subsets and the expression of B cell activation markers (CD80, CD86, PD1, CD40L) from a total of 71 SLE patients and 69 normal healthy volunteers. *In vitro* mechanistic studies and imaging flow cytometry were also performed to better understand the particular B cell phenotype identified in African American SLE patients.
Results. We found that B cells expressing the activation markers CD86, CD80, PD1 and CD40L, as well as CD19+CD27-IgD- double negative B cells, were enriched in African American patients vs. patients of European ancestry. In addition to increased expression of CD40L, surface levels of CD40 on B cells were lower, suggesting the engagement of the CD40 pathway. *In vitro* experiments confirmed that CD40L expressed by B cells could lead to CD40 activation and internalization on adjacent B cells.
Conclusions. To conclude, these results indicate that compared to European American patients, African American SLE patients present with a particularly active B cell component, possibly via the activation of the CD40-CD40L pathway. These data may help guide the development of novel therapies.

Key words: African American, B cell,CD40

S6:04

EFFECT OF B LYMPHOCYTE STIMULATOR AND ITS INHIBITION ON ENDOTHELIAL PROGENITOR CELLS AND MATURE ENDOTHELAL CELLS

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Objective. Endothelial dysfunction represents the earlier and reversible stage of atherosclerosis. Circulating endothelial progenitor cells (EPCs) are bone marrow-derived cells able to differentiate into mature endothelial cells, whose impairment is associated with endothelial dysfunction. Aim of the study was to evaluate the effect of BLyS and its inhibition with Belimumab (BLM) on EPCs both *in vitro* and *ex vivo*, in Systemic Lupus Erythematosus (SLE) patients receiving BLM. Moreover, we tested the effect of BLyS and BLM on mature endothelial cells.
Design and Method. We enrolled SLE patients starting BLM and matched controls, without cardiovascular disease.
Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll density-gradient centrifugation and incubated with fluorescein isothiocyanate-labeled anti-CD34 monoclonal antibodies and phycoerythrin-labeled anti VEGF-R2/KDR; acquisition was performed by flow cytometry: EPCs were defined as CD34/KDR double-positive cells.
For *in vitro* studies, recovered EPC isolated from healthy donors' PBMC were plated on dishes coated with human fibronectin. Apoptosis was investigated after 6, 12 and 24 hours of incubation with BLyS at different concentration – 5, 20 and 100 ng/ml – and re-evaluated after 6 hours of co-incubation with BLM at 173 and 300 μg/ml. The same experiments were repeated with the human umbilical vein cell line EA.hy926.
Disease activity was assessed by SLEDAI-2K.
Results. We enrolled 18 female patients (mean age 41.3±10.1 yrs, mean disease duration 19.2±9.2 yrs). Number of EPCs was significantly lower in the whole SLE population compared to NHS (p=0.004). Of the 18 patients, 10 (mean age 45.6±10.2 yrs, mean disease duration 17.8±10.8 yrs) started BLM for refractory disease (mean baseline SLEDAI 8.4±2.6). After 4 and 12 weeks SLEDAI 2K tended to decrease (p=ns). Baseline EPCs number was significantly lower compared to NHS (p=0.005). After 4 weeks, mean EPCs number increased from 0.013±0.016 to 0.021±0.016 (p=0.012 vs baseline; p=n.s. vs NHS). At week 12, EPCs did not differ significantly compared to week 4 nor to baseline.
We observed that 20 ng/ml of BLyS induced apoptosis of EPCs after 6 hours of incubation; this effect was reverted by the addiction of 173 and 300 μg/ml of BLM. BLM alone didn't induce apoptosis of EPCs. Similarly, after 6 hours of incubation with 20 ng/ml of BLyS we detected an increase in EA.hy926 apoptosis that was reverted by co-incubation BLM.
Conclusions. Our results confirm a reduction of EPCs number in SLE patients compared to NHS. In SLE patients who started BLM we detected a significant increase in EPCs after the first two infusion of BLM. *In vitro* data support a direct role of BLM by demonstrating a pro-apoptotic effect of BLyS that was reverted by the addition of the human anti-BLyS both in EPCs and EA.hy926 culture. These results further suggest a contribution of BLyS and B cells in the promotion of atherosclerosis.

Key words: endothelial progenitor cells, belimumab, endothelial function

S6:05

EFFECT OF SERPINB3 TREATMENT ON THE DEVELOPMENT OF GLOMERULONEPHRITIS IN NZB/NZW F1 MICE

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Objective. SerpinB3 (Serin Protease Inhibitor) is a member of the ovoalbumin serin protease inhibitor family. It is a pleiotropic intracellular protein, which exerts antiapoptotic effects on different cell types. It is downregulated in B cells of patients with systemic lupus erythematosus.
We studied the effect of SerpinB3 administration on the disease course in a murine model of lupus-like nephritis.
Design and Method. Two groups of 11-week-old NZB/NZW F1 female mice (12 mice each) were intraperitoneally injected with human recombinant SerpinB3 7.5μg in 100μl PBS (SerpinB3-treated mice, group 1) or 100μl PBS (control mice, group 2) twice a week prior to disease onset until natural death (preventive approach). Two groups of 8-week-old NZB/NZW F1 mice (10 mice each) were injected with SerpinB3 15μg in 200μl PBS (SerpinB3-treated mice, group 3) or 200μl PBS (control mice, group 4), twice a week after the onset of proteinuria >30mg/dl until natural death (therapeutic approach). Mice were monitored weekly for proteinuria by multistick analysis, and monthly for anti-double stranded DNA (dsDNA) and anti-C1q antibodies by ELISA tests. Proteinuria-free survival and global survival rates were evaluated. Mann-Whitney and Mantel-Cox statistics were applied.

Table I. Comparison (Mann-Whitney U test) of circulating autoantibodies levels and proteinuria levels betweeen Group 1 (SerpinB3-injected mice) and Group 2 (PBS-injected mice), expressed as the median (25th-75th percentile) OD of the double of every serum.

	Group 1	Group 2	Group 1 vs. Group 2 P
Anti-dsDNA			
W17	0.037 (0.025-0.061)	0.038 (0.033-0.081	n.s.
W21	0.074 (0.045-0.104)	0.188 (0.136-0.242)	<0.0001
W25	0.103 (0.077-0.104)	0.337 (0.093-0.414)	0.035
W29	0.338 (0.304-0.480)	0.570 (0.412-0.665)	0.034
W33	0.437 (0.352-0.600)	0.572 (0.397-0.614)	n.s.
Anti-C1q			
W17	0.131 (0.120-0.210)	0.132 (0.125-0.198)	n.s.
W21	0.126 (0.117-0.212)	0.254 (0.179-0.488)	0.004
W25	0,226 (0.218-0.271)	0.337 (0.321-0.491)	<0.0001
W29	0.370 (0.309-0.457)	0.828 (0.436-0.903)	0.018
W33	0.636 (0.535-0.780)	0.611 (0.423-0.882)	n.s.
Proteinuria			
W21	0 (0.00-0.00)	0 (0.00-15.00)	0.002
W23	0 (0.00-0.00)	15 (15.00-97.50)	<0.0001
W25	15 (0.00-18.75)	22.50 (15.00-97.50)	n.s.
W27	30 (26.25-47.50)	165 (26.25-2000.00)	n.s.
W29	65 (30.00-150.00)	300 (100.00-2000.00)	0.034
W33	300 (150.00-2000.00)	1150 (300.00-2000.00)	n.s.

Footnotes: anti-dsDNA: antibodies against double stranded DNA; anti-C1q: antibodies against complement fragment 1; W: week of age; n.s.: not significant.

Results. In the preventive approach, anti-dsDNA and anti-C1q autoantibodies appeared later and at lower titers in group 1 compared with group 2, reaching statistically significant difference from week 21 to week 29 (anti-dsDNA: week 21, $p<0.0001$; week 25, $p=0.035$; week 29, $p=0.034$; anti-C1q: week 21, $p=0.004$; week 25, $p<0.0001$; week 29, $p=0.018$) (Table I).
In the therapeutic approach, autoantibodies were significantly downregulated in group 3 compared with group 4 after 3 weeks of treatment (anti-dsDNA, $p=0.008$; anti-C1q, $p=0.016$). Proteinuria levels were lower in SerpinB3-injected mice than in controls, yet statistical significance was reached only in the preventive approach (week 21, p=0.002; week 23, $p<0.0001$; week 29, $p=0.034$) (Table I). Both preventive and therapeutic administration of SerpinB3 significantly delayed proteinuria ($p=0.017$ and $p=0.028$, respectively) and prolonged survival ($p=0.022$ and $p=0.033$, respectively) in SerpinB3-treated mice compared with untreated ones.
Conclusions. Treatment with SerpinB3 seems to exert either a protective or therapeutic effect against the development of glomerulonephritis in NZB/NZW F1 lupus-prone mice.

Key words: SerpinB3, murine model, lupus nephritis

S6:06

SLEDAI-2K AND POLYARTHRITIS ARE THE BEST PREDICTORS OF RESPONSE TO BELIMUMAB IN PATIENTS WITH ACTIVE SLE IN CLINICAL PRACTICE SETTING: DATA FROM MULTICENTRIC ITALIAN STUDY

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Objective. To investigate effectiveness and identify predictors of response to belimumab in patients with active systemic lupus erythematosus (SLE) in clinical practice setting.
Design and Method. One hundred and forty active SLE (ACR criteria) patients, from 8 Italian prospective lupus cohorts, were treated with belimumab (10 mg/kg day 0, 14, 28 and then every 28 days), as add-on therapy. They were 131 females and 9 males, mean age 41.2±10.4 years, mean disease duration 12.9±8.4 years. All had positive anti-dsDNA antibody and low C3 and/or C4. SLEDAI-2K, anti-dsDNA, C3, C4, and prednisone daily dose were recorded at baseline, at month 3, 6, 9, 12, 18 and 24 months. Disease activity score (DAS-28), 24-hours proteinuria, CLASI (Cutaneous LE Disease Area and Severity Index) were recorded to evaluate organ response. Anti-dsDNA levels were measured by enzyme linked immunosorbent assay (ELISA) in 76 patients, indirect immunofluorescence (IFI) in 36 patients, Farr assay in 28 patients.
The following variables were included in the univariate and multivariate analysis to determine baseline predictors of response according to SLE Responder Index (SRI) at 12 and 24 monthsmonths: disease activity pattern (relapsing remitting or chronic active), SLEDAI-2K >=10, high anti-dsDNA levels (>300 KIU/L in ELISA, >21 UI/ml in Farr assay, >1:320 in IFI), prednisone dose >7,5 mg/day, concomitant immunosuppressants (yes/no) or antimalarials (yes/no), polyarthritis, skin rash, glomerulonephritis (GN), hematologic involvement. Pattern of disease activity was identify as chronic active disease in patients with a SLEDAI-2K>=2 excluding serology in at least two out of the three annual visits and relapsing-remitting disease in patients with a SLEDAI-2K>=2 excluding serology in one out of three annual visits.
Results. Mean follow-up period was 15.2±10.1 months (range 1-33). Active manifestations which required the use of belimumab were polyarthritis in 45.6%, skin rash in 24.3%, GN in 13.6%, hematologic involvement in 13.6% of patients. A significant decline in SLEDAI-2K, prednisone daily dose, anti-dsDNA (measured by ELISA), DAS-28, CLASI, 24-hour proteinuria, and a significant increase in C3 and white cell count was found at 24 months by analysis of covariance (ANOVA) (Table).
SRI was achieved by 74.0% and 70.0% of patients at 12 and 24 months, respectively. Baseline predictors of response at 12 and 24 months were: SLEDAI-2K >=10 ($p=0.032$ and $p=0.030$, respectively), polyarthritis ($p<0.0001$ and $p=0.004$, respectively), absence of GN ($p=0.003$ and $p=0.005$, respectively). SLEDAI-2K ($p=0.02$) and polyarthritis ($p=0.03$) were independent predictors of response at 12 months by multivariate analysis.
Conclusions. Our data confirms the effectiveness of belimumab in clinical practice setting. High disease activity and polyarthritis were the best predictors of response in our cohort of patient with clinically and serologically active SLE.

Key words: belimumab, clinical practice setting, predictor of response

Table. Variation of clinical and serologic disease activity variables in 140 patients with active lupus treated with belimumab.

	N° pts	Baseline	6 Months pts: 115	9 months pts: 92	12 months pts:82	18 months pts:57	24 months pts:40	*p**
SLEDAI-2K	140	8.65±3.62	5.23±3.10	4.44±2.95	3.96±2.76	4.19±2.95	3.85±2.78	**<0.0001**
C3 (g/l)	140	0.72±0.23	0.77±0.19	0.77±0.18	0.79±0.20	0.79±0.18	0.85±0.21	**<0.0001**
C4 (g/l)	140	0.12±0.07	0.15±0.16	0.17±0.17	0.16±0.07	0.17±0.09	0.17±0.06	0.063
Prednisone daily dose (mg/day)	140	10.55±6.38	6.82±4.04	5.82±3.74	4.60±2.55	4.41±3.66	3.91±3.99	**<0.0001**
Anti-dsDNA (ELISA, KIU/L)	76	423.4±907.2	174.7±239.6	171.26±246.0	156.9±255.8	137.1±194.5	104.7±118.3	**0.021**
Anti-dsDNA (FArr, UI/mL)	28	104.2±204.9	44.2±50.8	42.1±53.2	41.7±70.9	38.4±54.2	21.1±23.3	0.265
DAS-28	80	4.00±1.00	2.67±1.06	2.18±0.95	2.19±0.61	2.0±0.56	1.84±0.39	**<0.0001**
CLASI	44	4.91±3.48	2.18±3.18	1.47±2.54	1.oo±1.59	1.79±2.39	1.29±2.13	**<0.0001**
24-h proteinuria (g/die)	31	1.13±0.70	0.91±0.81	0.81±0.75	0.70±0.57	0.73±0.79	0.71±0.67	**0.018**

*p calculated using analysis of covariance /ANOVA) at month 24.
SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; anti-dsDNA: anti-double stranded DNA; CLASI: Cutaneous Lupus erythematosus Area and Severity Index; DAS-28: disease activity score-28 joints; ELISA: Enzyme-Liked ImmunoSorbent Assay; pts: patients.

S7: SLE and clinical trials: past and future

S7:04

ONSET AND DURABILITY OF EFFICACY OF BELIMUMAB ADMINISTERED SUBCUTANEOUSLY PLUS STANDARD OF CARE MEDICATIONS TO PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IN A PHASE III TRIAL

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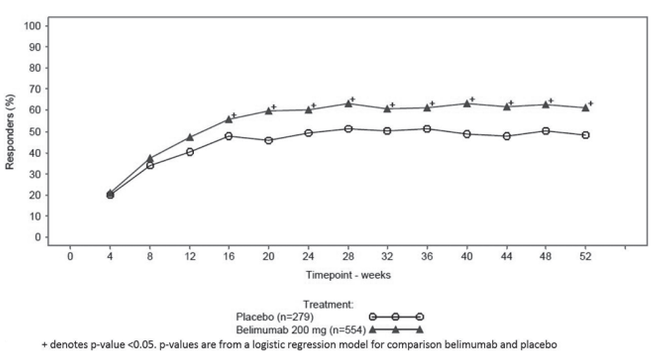
Objective. BLISS-SC (BEL112341; NCT01484496), a randomised, double-blind, placebo-controlled trial, assessed efficacy and safety of subcutaneous belimumab (BEL) plus standard of SLE care (SoC) in patients with active SLE. Time to onset and durability of BEL efficacy over 52 weeks was examined.
Methods. Patients with SELENA-SLEDAI (SS) score ≥8, receiving stable SoC (≥30 days) were randomised (2:1) to weekly BEL 200 mg or placebo (PBO), subcutaneously (prefilled syringe), plus SoC. Primary endpoint (Week 52) was SLE Responder Index (SRI: ≥4-point SS reduction, no worsening [<0.3-increase] in Physician's Global Assessment, 0 new BILAG A/≤1 new BILAG B organ domain scores, vs baseline). Various comparisons of SRI response over 52 weeks were conducted to assess onset/durability. Safety was assessed by adverse events (AEs).
Results. Baseline characteristics were similar between groups: mean (standard deviation [SD]) age BEL 38.1 (12.1), PBO 39.6 (12.6) years; median (range) disease duration BEL 4.3 (0–35), PBO 4.6 (0–38) years; mean (SD) SS BEL 10.5 (3.2), PBO 10.3 (3.0). SRI response occurred in both groups by Week 4, and was significantly greater for BEL vs PBO from Weeks 16–52 (Figure). SRI response maintained through Week 52 was more likely with BEL vs PBO (hazard ratio, 1.48 [CI 1.21, 1.81], p=0.0001). At Week 52 a greater proportion in the BEL group vs PBO maintained a response post baseline for ≥1 month (55.2% vs 41.6%, p=0.0002), ≥10 months (21.1% vs 12.9%, p=0.0043) and at all timepoints in between. Mean (standard error) longest SRI response was BEL 193.9 (7.2) vs PBO 169.3 (8.8) days (p=0.005). Withdrawals (BEL 16.7%, PBO 23.6%) included: AEs BEL 7.2%, PBO 8.9%; patient request BEL 2.2%, PBO 5.4%; lack of efficacy BEL 2.7%, PBO 3.6%. Serious AEs (BEL 10.8%, PBO 15.7%) included: infections/infestations BEL 4.1%, PBO 5.4%; renal/urinary BEL 1.4%, PBO 2.5%; nervous system BEL 1.4%, PBO 2.1%. Incidence of depression/suicide/self-injury was BEL 3.1%, PBO 3.6%. Five deaths occurred: BEL 0.5% (three infections), PBO 0.7% (one haematologic, one vascular).



Conclusion. Subcutaneous BEL plus SoC significantly improved SRI response from weeks 16–52 vs PBO plus SoC. Safety with BEL plus SoC was similar to PBO plus SoC.

Key words: systemic lupus erythematosus, clinical trial, belimumab

S7:06

LOW-DOSE IL-2 THERAPY IN SLE: RESULTS FROM A COMBINED PHASE I/IIA CLINICAL TRIAL

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Objective. Interleukin-2 (IL-2) is crucial for the growth and survival of regulatory T cells (Treg), and thus for the control of autoimmunity. In previous studies we have proven the significance of an acquired IL-2 deficiency and related Treg defects in the pathogenesis of systemic lupus erythematosus (SLE). Accordingly, we showed that compensation of IL-2 deficiency by IL-2 therapy corrects associated Treg defects and ameliorates already established disease in lupus-prone mice (1). Proceeding to a clinical translation of IL-2 therapy for SLE, we recently reported a rapid and robust reduction of disease activity in parallel to a remarkable expansion of the Treg population by low-dose IL-2 therapy in one patient with refractory SLE (2). In addition, we showed that Treg defects in SLE patients are associated with IL-2 deficiency, and can be selectively corrected *in vitro* and *in vivo* with low doses of IL-2 (3). Together, these studies provided the rationales for the clinical implementation an IL-2-based immunotherapy for the treatment of SLE with the aim to restore Treg activity and thus to re-establish endogenous mechanisms of immune tolerance which can counteract autoimmunity.
Here we present current results from the ongoing single-center phase I/IIa clinical trial evaluating the safety, tolerability, immunological responses and the clinical efficacy of a cyclic and subcutaneously applied low-dose IL-2 therapy in patients with refractory SLE (PRO-IMMUN).

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Key words: interleukin-2, regulatory T cell, immunotherapy

S8: Traditional syntetic drugs in SLE

S8:04

RESPONSE TO A COMBINED HYDROXYCHLOROQUINE-QUINACRINE TREATMENT IN SLE WITH CUTANEOUS AND/OR JOINT DISEASE

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Objective. To evaluate the efficacy of combined therapy with hydroxychloroquine (HCQ) and quinacrine of SLE patients with cutaneous and/or articular activity unresponsive to previous therapies.
Design and Method. Our aim was to evaluate the clinical response to quinacrine addition in a total of 37 SLE patients having proved unresponsive to treatment with at least two drugs including glucocorticoids (GC) and HCQ. The following variables were recorded: epidemiological features, smoking behaviour, duration of disease, autoantibody profile, clinical features, previous treatments, clinical response (based on clinical judgement), and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at 0-3-6-12 months and at the end of follow-up. Independent predictors of response were identified by logistic regression.
Results. We included a total of 37 patients with refractory disease to either of the following drug combinations: HCQ+ glucocorticoids (GC) (n=8) HCQ+ glucocorticoids + retinoids (n=2), HCQ+ one nonbiologic immunosuppressant (n=1), HCQ+ GC+ at least one immunosupressive agent (n=25) or HCQ+GC+ one immunosupressive drug+ one biologic drug (n=1). The main clinical features of the cohort are displayed in Table I.
Globally, 89% of patients showed either complete response (CR) or partial response (PR) based on clinical judgement. Regarding joint disease, 90% were on CR+/-PR at the end of follow-up vs 87% of patients with skin involvement. A statistically significant decrease in the CLASI was seen at all points of follow-up. Interestingly, the rate of CR was significantly higher in smokers than non-smokers (OR 5, 95%CI, p=0.024). No other epidemiological, therapeutic, clinical or serological variable were identified as response predictors.

VARIABLE	PERCENTAGE	
Demographic features		
-Female (%)	91.9	(n=34
-Disease duration (median)	10	(RI=10)
-Age (media)	38.22	(SD=10.64)
-Smokers	35.14	(n=13)
Serologic features		
-anti-Sm (%)	21.62	(n=8)
-Anti ADN (%)	45.95	(n=17)
-Anti Ro (%)	37.84	(n=14)
-Hypocomplementemia (%)	40.54	(n=15)
Indication for combined therapy		
-Cutaneous (%)	43.4	(n=16)
-Joint disease (%)	40.54	(n=15)
-Both (%)	16.22	(n=6)
Type of cutaneous lupus		
-SACL (%)	45.45	(n=10)
-Discoid (%)	40.91	(n=9)
-Profundus (%)	4.55	(n=1)
-Other (%)	9.09	(n=2)
Previous medication		
-HCQ (%)	100	(n=37)
-Prednisone (%)	94.5	(n=35)
-Prednisone dose at time 0 (mean)	6 mg	(SD 3.2)
-Prednisone dose at the end of follow-up	3.7 mg	(SD 2.2)
-MTX (%)	64.86	(n=24)
-MTX dosis (mean)	15 mg/w	(SD 4.5)
-MMF (%)	11.11	(n=4)
-MMF dose (mean)	1600 mg	(SD 547)
-AZA (%)	16.22	(n=6)
-AZA dose (mean)	95 mg	(SD 18)
-CFM (%)	2.7	(n=1)
-Tacrolimus (%)	2.7	(n=1)
-Belimumab (%)	5.4	(n=2)
-Retinoids (%)	5.4	(n=2)

Conclusions. In the setting of refractory skin and/or joint disease, the addition of quinacrine to the previous therapy including HCQ proved to be effective in reducing disease activity. The fact that smokers responded better than non-smokers opens the door to study whether the metabolism of quinacrine might be less influenced by smoking than that of HCQ.

Key words: quinacrine, hydroxychloroquine, combined therapy

S8:05

SURVIVAL OF PREDNISONE-FREE REMISSION IN SLE PATIENTS WITH SEROLOGICALLY ACTIVE CLINICAL QUIESCENT DISEASE

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Objective. To evaluate survival of prednisone (PDN) – free remission in systemic lupus erythematosus (SLE) patients and to investigate the potential predictors of disease flares.

Table I. Demographic and clinical variables in all patients and according to survival of prednisone-free remission.

	All patients	Patients maintaining PDN-free remission	Patients who flared	*p*-value
Patients, N	104	82	22	-
Female, N (%)	91 (87.5%)	69 (84.1%)	22 (100.0%)	0.046
Age in 2016, years, mean ± SD	18.69±10.81	18.88±11.14	18.0±9.71	0.723
Age at PDN-stop, years mean ± SD	39.08±11.2	39.32±11.27	38.18±10.68	0.844
Disease duration, months, mean ± SD	15.83±8.52	15.72±8.20	16.0±9.71	0.817
Duration of corticosteroid therapy, months, mean ± SD	131.77±89.74	128.34±88.3	140.73±96.16	0.607
Duration of remission before PDN-withdrawal, months, mean ± SD	36.80±33.01	38.24±34.95	31.91±23.51	0.765
Duration of remission after PDN-withdrawal, months, mean ± SD	48.52±43.29	61.12±39.69	-	-
Time to flare, months, mean ± SD	4.25±10.14	-	19.81±13.14	-
SDI >3, (%)	10 (9.6%)	8 (9.8%)	2 (9.1%)	0.925
Positive anti-ds-DNA abs and-or low C3/C4, N (%)	89 (85.6%)	68 (82.9%)	21 (95.5%)	0.138
Systemic involvement, N (%)	61 (58.7%)	51 (62.2%)	10 (45.5%)	0.474
Skin rashes, N (%)	36 (37.7%)	22 (26.8%)	13 (59.1%)	0.004
Arthritis, N (%)	69 (66.3%)	51 (62.2%)	18 (81.8%)	0.084
Serositis, N (%)	16 (15.4%)	13 (15.9%)	3 (13.6%)	0.798
Glomerulonephritis, N (%)	65 (62.5%)	53 (64.5%)	12 (54.5%)	0.385
Trombosis, N (%)	12 (11.5%)	12 (14.6%)	0 (0%)	0.056
Neuropsychiatric manifestations, N (%)	10 (9.6%)	8 (9.8%)	2 (9.1%)	0.925
Vasculitis, N (%)	6 (5.8%)	4 (4.9%)	2 (9.1%)	0.452
Haematologiccal involvement, N (%)	25 (24.0%)	17 (20.7%)	8 (36.4%)	0.128
Concomitant immunosuppressive treatment, N (%)	41 (39.4%)	32 (39.0%)	9 (40.9%)	0.872
Flare, N (%)	22 (21.2%)	0.0	22 (100.0%)	-

PDN: prednisone; SD: standard deviation; SDI: SLICC/American College of Rheumatology Damage Index.

Design and Method. Inclusion criteria were: (1) Diagnosis of SLE according to American College of Rheumatology (ACR) Classification Criteria of SLE; (2) Caucasian ethnicity; (3) Serologically active clinical quiescent disease (SACQ) at the time of PDN-withdrawal; (4) Stop of PDN treatment between 2010 and 2015;(5) At least two visits per year between January 2010 and December 2015. Disease activity was assessed according to SLE Disease Activity Index-2000 (SLEDAI-2K). Damage was measured by the SLICC/American College of Rheumatology Damage Index (SDI). Flares were defined according to Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI criteria. We evaluated whether gender, age, age at PDN-stop, disease duration, duration of corticosteroid therapy, duration of remission before and after PDN withdrawal, time to flare, SLICC/American College of Rheumatology Damage Index (SDI) – score >3, positive anti-dsDNA antibodies (abs) and-or low C3/C4, type of SLE-involvement and concomitant immunosuppressive treatment could be predictors of flare. Multivariate logistic regression analysis was run to investigate the predictors of flare. Covariates included in the analysis were all variables reaching $p<0.20$ in the univariate analyses.

Results. Among 400 patients evaluated, 104 (26%) fulfilled inclusion criteria. Baseline characteristics are reported in Table I. Twenty-two (21.2%) patients flared. Mean time to flare was 4.25±10.14 months. Types of flare were 7 renal, 7 articular, 4 cutaneous, 2 haematological, 1 serositic and 1 neurological. Twenty-six (25%) patients achieved complete remission and 56 (53.8%) remained in SACQ disease. Variables included in the multivariate logistic regression analysis were: positive anti-dsDNA abs and-or low C3/C4, skin, articular and haematological involvement. Skin involvement resulted predictive of flare (OR 3.07, 95% CI 1.11-8.53, P 0.031) as reported in Table II.

Table II. Risk of flare in prednisone-free remission. Multivariate regression analysis.

	OR (95% C.I.)	*p*-value
Skin involvement	3.07 (1.11;8.53)	0.031
Articular involvement	2.75 (0.80;9.44)	0.108
Haematological involvement	1.89 (0.62;5.73)	0.261
Positive anti-ds-DNA abs and-or low C3/C4	3.17 (0.37;27.05)	0.292

OR: Odds Ratio; C.I.: Confidence Interval; SDI: SLICC/American College od Rheumatology Damaage Index.

Conclusions. In SLE patients who stopped corticosteroid therapy, previous skin involvement could be a predictor of flare.

Key words: prednisone, remission, survival

S8:06

AURION STUDY: 12 WEEK DATA OF MULTI-TARGET THERAPY WITH VOCLOSPORIN, MMF AND STEROIDS FOR LUPUS NEPHRITIS

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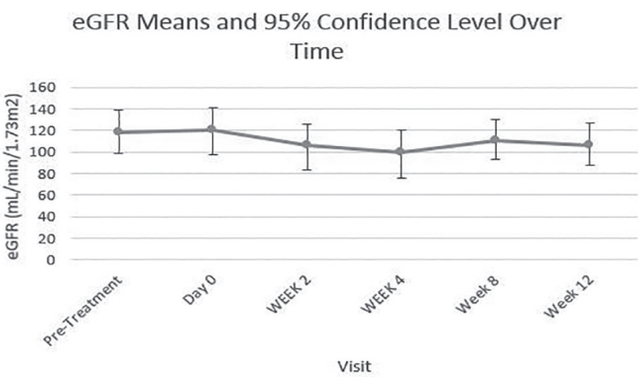
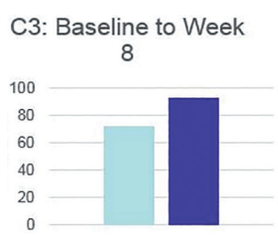
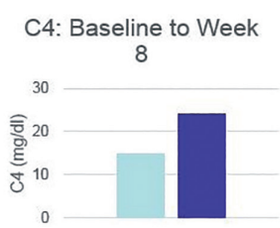
Objective. In lupus nephritis (LN), complete (CR) or partial remission (PR) is associated with better patient and renal survival. Studies demonstrate that subjects who did not achieve an early reduction in proteinuria of greater or equal to 25%were unlikely to achieve even PR. Recent studies suggest that a combination of calcineurin inhibitors (CNis), MMF and steroids may be effective in LN patients. Voclosporin (VCS) is a next generation CNi with a predictable pharmacokinetic-pharmacodynamics profile. This study, AURION, is the first reported pilot study of VCS in active LN assessing the ability of biomarkers at 8 weeks to predict clinical response over 24 and 48 weeks in subjects taking voclosporin in combination with MMF and steroids. We report 12-week data on patients to date.
Design and Method. Eligibility criteria include: biopsy-proven LN; SLE by ACR criteria; UPCr of >1.0mg/mg (Class III and IV) or >1.5mg/mg (Class V); and CKD-EPI eGFR>45ml/min/1.72m^2. VCS 23.7mg po BID is administered in combination with MMF1-2g and a reducing course of corticosteroids. eGFR was assessed at each visit using the CKD-EPI formula, along with UPCr assessments at each visit and biomarker (C3,C4 and anti-ds DNA)data at regular intervals. Proteinuria reduction is presented for subjects enrolled in this pilot study, together with renal function and biomarkers of lupus nephritis.
Results. A mean proteinuria reduction of 59% is observed at 12 weeks compared to baseline. 5 out of 9 subjects who have reached 12 weeks report CR as defined by UPCr <0.5 mg/mg. Some reduction in proteinuria is seen in 7 out of 9 subjects with improvements in C3, C4 and anti-ds DNA also reported. Stable renal function is also seen, with all values within normal range. 2 subjects experienced increased BP which resolved on reduction of the voclosporin dose. One of those subjects also experienced anemia secondary to MMF administration.
1 subject experienced hirsutism which resolved with voclosporin dose reduction.
1 subject's serum creatinine increased secondary to disease progression.
Conclusions. Over 50% of subjects demonstrate complete renal remission by 12 weeks. Despite the profound drop in proteinuria, there was little impact on renal function. All of the other pre-specified eight week biomarkers of active lupus nephritis (LN) have also improved and are trending towards normalization. These biomarkers have also been shown to be predictive of a positive clinical response at 24 weeks.
Preliminary results from this pilot study support the hypothesis that multi-target therapy with VCS in combination with MMF and steroids appears to be beneficial, with preservation of renal function, and well tolerated in subjects with active LN.

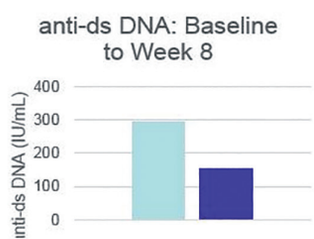
Key words: nephritis, multi-target therapy, clinical trials

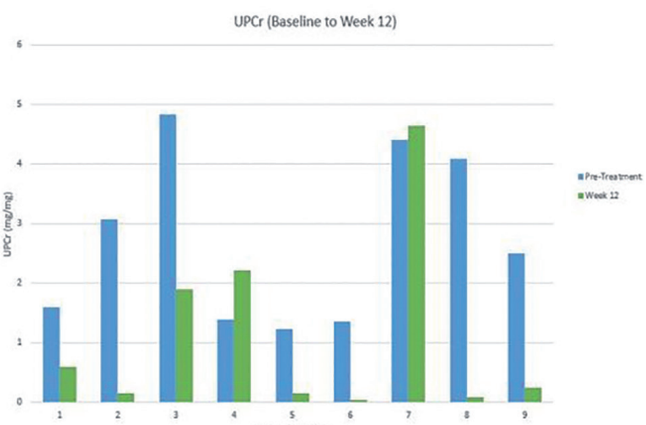
Demographics		(n=10)
Age (years)		28.6 ± 5.1*
Race		Asian
Sex (F/M)(%)		100/0
Time from SLE to LN diagnosis (years)		2.2 ± 3.3*
Time from SLE to study entry (years)		6.1 ± 3.0*
LN Class at study entry (n,%):	Class III	4 (40%)
	Class IV	3 (30%)
	Class V	3 (30%)
MMF Naïve (%)		40%
eGFR at study entry (ml/min/1.73m²)		118 ± 28*
Urine Protein/Creatinine Ratio		2.6 ± 1.5*
* mean ± SD		











S9: SLE genetics

S9:04

A POLYMORPHISM UPSTREAM MIR1279 GENE IS ASSOCIATED WITH PERICARDITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS AND CONTRIBUTES TO DEFINITION OF A GENETIC RISK MODEL PROFILE

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Objective. MicroRNAs have emerged as important regulators of gene expression in post-transcriptional level. These are a class of small non-coding molecules, which could contribute to the pathogenesis of autoimmune diseases, including systemic lupus erythematosus (SLE). Recently, it has been demonstrated that the rs1463335 SNP in MIR1279 gene region was associated with decreased levels of TRAF3IP2 expression. We have previously demonstrated an association between TRAF3IP2 polymorphisms and SLE, especially with the development of pericarditis (1). Thus, we aimed to investigate the role of the MIR1279 rs1463335 SNP in SLE, with particular regards to pericarditis development. Furthermore, we aimed at constructing a pericarditis genetic risk profile for SLE patients considering others risk alleles that we had previously found associated with pericarditis development (1, 2).
Design and Method. We recruited 315 Italian SLE patients and 278 healthy controls. Rs1463335 SNP, located upstream MIR1279 gene, was analyzed by allelic discrimination assay. MIR1279 gene was further sequenced in 50 patients. Genotyping of rs7574865 (STAT4), rs2542151 (PTPN2), rs2241880 (ATG16L1) and rs33980500 (TRAF3IP2) SNPs were also performed. A case/control association study and a genotype/phenotype correlation analysis were performed and a risk profile model for pericarditis in SLE was built.
Results. The full sequencing of the MIR1279 gene in SLE patients did not reveal any novel or known variation. The variant allele of the rs1463335 SNP was significantly associated with susceptibility to pericarditis (p=0.017, OR=1.67). Patients carrying the A allele were more susceptible to develop the pericarditis with an allele-additive effect: patients carrying the variant homozygous genotype have a higher risk than patients carrying the heterozygous genotype (p=0.013, OR=3.28 vs p=0.06, OR=2.4, respectively). A risk profile model for pericarditis considering the risk alleles of MIR1279 and other three genes (STAT4, PTPN2 and TRAF3IP2) showed that patients with 4 or 5 risk alleles have a significantly higher risk to develop pericarditis (OR=4.09 with p=0.001 and OR=6.04 with p=0.04 respectively). AntiSm antibodies were the only parameter associated with the development of pericarditis. A multivariate analysis by binary regression analysis, considering as dependent variable the presence/absence of pericarditis and as independent variables all the studied SNPs associated with pericarditis, was performed. In a stepwise approach including anti-Sm, MIR1279, STAT4, TRAF3IP2 and PTPN2 SNPs, this model explains about 25% (R2 Cox &Snell) of the variability involved in the susceptibility to pericarditis.
Conclusions. We describe for the first time the contribution of a MIR1279 SNP in pericarditis development in SLE patients and a genetic risk profile model useful to identify patients more susceptible to develop pericarditis in SLE. This approach could help to improve the prediction and the management of this manifestation.

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Key words: MIR1279, pericarditis, risk profile

S9:05

ALLELE-SPECIFIC BINDING DIFFERENCES OF FOX TRANSCRIPTION FACTORS TO IKZF3 RISK ALLELES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. One of the biggest challenges we face in genetics is identifying causal-alleles with functional significance at susceptibility loci possessing extended risk-haplotypes carrying many tag-SNPs, often after several rounds of replication and/or meta-analysis. We present a novel strategy to prioritise tag-SNPs with the highest likelihood of biological relevance for laboratory functional studies. This strategy involves trans-ancestral mapping of risk-haplotypes, MAF-exclusion-mapping of discordant variants, with epigenetic annotation/identification of allele-specific transcription factor binding sites, using data from public databases such as RoadMap, ENCODE and HaploRegv4, as a surrogate for causality. We illustrate the utility of our approach using the Ikaros transcription factor (TF) IKZF3, with an associated European (EUR) SLE haplotype (208kb) extending over multiple genes, carrying 201 tag-SNPs, from the bidirectional IKZF3 3' flanking-region into the upstream-region of ORMDL3.
Design and Method. Align IKZF3 haplotypes from our large EUR GWAS and five 1000 Genomes super-populations. Compare EA-African MAF to delineate discordant tag-SNPs. Identify co-localised epigenetic marks in blood cell-types (cut-off:-log10P>20 RoadMap) and TF binding-sites (TFBS) with predicted allele-specific differences in binding intensity (LOD>3 HaploRegv4).
Results. Trans-ancestral mapping reduced the risk-haplotype by >50% to 111kb and the tag-SNPs by 28% to 150. Filtering these SNPs on AFR MAF yielded 31 variants absent/very low MAF in AFR. Epigenetic annotation revealed six variants with co-localised strong epigenetic marks/predicted allele-specific changes in TF binding-intensity. The two SNPs showing the strongest chromatin modification (H3K27ac), in only primary B-, T-, Th-, Treg- and NK cells from peripheral blood, are predicted to change the binding-intensity of two Fox-family TFs: rs111678394 (IKZF3-ZPBP2 bidirectional promoter, long IKZF3 isoform) reduces the Foxi1 binding-affinity and rs113730542 (intron 1, shorter IKZF3 isoform) increases the Fox binding-affinity.
Conclusions. These data demonstrate the power of trans-ancestral exclusion-mapping/epigenetic annotation in defining identifying functionally-relevant alleles from extended haplotypes. Our hypothesis is that IKZF3 deficiency is pathogenic for lupus, since Ikzf3-/- mice develop autoimmunity. Cell-type specific reduced Foxi1/increased Fox binding at different IKZF3 isoforms, may influence the isoform balance. The shorter isoform, a defective TF, cannot bind DNA. One potential mechanism for IKZF3 dysfunction in lupus may be Fox-dependent changes in functional IKZF3 TF activity levels. Further investigation is required to confirm this finding.

Key words: Ikaros transcription factor, transancestral exclusion map, epigenetics

S9:06

SINGLE CELL GENE EXPRESSION STUDIES IN LUPUS PATIENT MONOCYTES REVEAL NOVEL PATTERNS REFLECTING DISEASE ACTIVITY, INTERFERON, AND MEDICAL TREATMENT

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Objective. Our previous studies have shown that different cell types from the same sample demonstrate diverse gene expression, and important findings can be masked in mixed cell populations. In this study, we examine single cell gene expression in SLE patient monocytes and determine correlations with clinical features.
Design and Method. CD14++CD16- classical monocytes (CLs) and CD14dim-CD16+ non-classical monocytes (NCLs) from SLE patients were purified by magnetic separation. The Fluidigm single cell capture and Rt-PCR system was used to quantify expression of 87 monocyte-related genes.
Results. Both CLs and NCLs demonstrated a wide range of expression of IFN-induced genes, and NCL monocytes had higher IFN scores than CL monocytes. Unsupervised hierarchical clustering of the entire data set demonstrated two unique clusters found only in SLE patients, one related to high disease activity and one related to prednisone use. Independent clusters in the SLE patients were related to disease activity (SLEDAI 10 or greater), interferon signature, and medication use, indicating that each of these factors exerted a different impact on monocyte gene expression that could be separately identified. A subset of anti-inflammatory gene set expressing NCLs was inversely correlated with anti-dsDNA titers (rho = -0.77, p=0.0051) and positively correlated with C3 complement (rho = 0.68, p=0.030) in the SLE patient group.
Conclusions. Using single cell gene expression, we have identified a unique gene expression patterns that reflect the major clinical and immunologic characteristics of the SLE patients which are not evident in bulk cell data, supporting the critical importance of the single cell technique.

Key words: interferons, gene expression, single cell

S10: Targets in SLE treatment

S10:04

THE PREDICTIVE EFFECT OF A RANGE OF DURATION OF REMISSION ON DAMAGE ACCRUAL IN SYSTEMIC LUPUS ERYTHEMATOSUS. RESULTS FROM A PROSPECTIVE MONOCENTRIC COHORT OF 293 PATIENTS

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Objective. To assess the prevalence of a range of durations of remission and its predictive effect on damage accrual in a cohort of Caucasian patients affected with systemic lupus erythematosus (SLE).
Design and Method. Caucasian patients diagnosed with SLE between 1990 and 2009 and quarterly seen from 2009 to 2015 were included in the study. Disease activity was assessed using the SLE Disease Activity Index-2000 (SLEDAI-2K) and damage using the SLICC/ACR Damage Index (SDI). Three levels of remission were defined, according to clinical disease activity, serological activity and treatment: complete remission, i.e. no disease activity in corticosteroid- and immunosuppressant-free patients; clinical remission off-corticosteroids, i.e. serologic active clinical quiescent (SACQ) disease in corticosteroid-free patients; clinical remission on corticosteroids, *i.e.* clinical quiescent disease with or without serological abnormalities in patients taking prednisone 1-5 mg/day. Five range of durations of remission were evaluated: a remission lasting 1, 2, 3, 4, 5 or more consecutive years. The impact of different levels and durations of remission on SDI accrual was evaluated by univariable and multiple logistic regression analysis. Statistical analysis was performed by the SPSS software for Windows (version 22.0).
Results. Two-hundred ninety three patients fulfilled inclusion criteria: 253 (86.3%) were female, mean±SD disease duration 11.1±7.8 years. During the 7-year follow-up, 113 patients (38.6%) achieved >=5-year remission, 26 (8.9%) 4-year remission, 45 (15.4%) 3-year remission, 47 (16.0%) a 2-year remission, and 27 (9.2%), 1-year remission. Thirty-five patients (11.9%) never achieved any remission during follow-up.
SDI increased less frequently in patients in remission for 2, 3, 4, or >=5 consecutive years (66.0%; 51.1%; 50%; 27.4%) compared with unremitted patients (88.6%, p=0.018 vs 2 years, p<0.001 for all other comparisons) as well as compared with patients with a remission lasting only 1-year (81.5%, p=0.051, p=0.010, p=0.021, p<0.001, respectively).
Mean damage accrual over the follow-up was 0.77±0.95. SDI mean increase was progressively lower in patients with a 2 (0.97±0.81), 3 (0.71±0.83), 4 (0.67±0.73), or >=5 (0.34±0.62) consecutive year remission. In addition, SDI was higher in unremitted patients (1.59±1.16), and 1-year remitted patients (1.71±1.30) compared with patients with 2-year (p=0.006 and p=0.017), 3-year (p=0.002 and p=0.004), 4-year (p<0.001 and p<0.001) and >=5-year remission (p<0.001 and p<0.001).
At multivariate analysis, a remission lasting at least 2 years was predictive of no damage accrual (2 year remission OR 0.228, 95% IC 0.061– 0.850, p=0.028; 3 years OR 0.116, 95% IC 0.031– 0.436, p=0.001; 4 years OR 0.118, 95% IC 0.027– 0.519, p=0.005; >=5 years OR 0.044, 95% IC 0.012– 0.159, p<0.001).
Conclusions. A disease remission of 2 consecutive years could be considered as a clinically meaningful target in the management of SLE patients, since it was associated with a significantly better outcome in terms of damage accrual.

Key words: remission, SLICC Damage Iindex, predictors of damage accrual

S10:05

A COMPLETE REMISSION LASTING AT LEAST ONE YEAR INFLUENCES THE OUTCOME IN PATIENTS AFFECTED BY SLE: RESULTS FROM A LARGE MONOCENTRIC COHORT

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Objective. The achievement of complete remission is an important goal in the treatment of patients with Systemic Lupus Erythematosus (SLE). Even though a consensus has been reached concerning its definition (complete absence of clinical and serological signs or symptoms of activity) and the acceptable treatment (only antimalarial drugs), several proposals have been suggested concerning the duration. The primary end-point of the present study was to analyze the frequency of complete remission lasting at least 1 year in a large monocentric SLE cohort. Secondly, we aimed at evaluating its association with different clinical and serological parameters and its impact on the chronic damage accrual.
Design and Method. We analyzed our database including SLE patients evaluated between September 2008 and December 2015. The following inclusion criteria were considered: (1) at least 4 revised American College of Rheumatology (ACR) Classification Criteria for SLE; (2) Caucasian ethnicity; (3) at least two visits/year between January 2011 and December 2015. The frequency of complete (clinical and serological) remission, defined as SLEDAI-2k=0, was evaluated in corticosteroid-free and immuno-suppressant-free SLE patients, considering acceptable only antimalarial drugs.
Results. Our database includes 658 SLE patients evaluated at least once. According with the inclusion criteria, we analyzed 179 SLE patients (M/F 13/166, mean age 46.3±12.7 years, mean disease duration 173.9±101.9 months). Twenty-seven patients (15.1%) experienced a complete remission for at least 12 months, with a mean duration of 37.5±15.8 months. Six patients experienced a prolonged complete remission lasting 5 years (4.6%). Remission SLE patients showed significantly lower frequency of renal involvement (29.0 vs 18.4, p=0.04) and low C3 and C4 serum levels (14.8% vs 36.8%, p=0.0005; 14.8% vs 33.5%, p=0.0002, respectively). Interestingly, the frequency and the severity of chronic damage, evaluated by SLICC, resulted significantly lower in patients achieving remission (11.1% vs 51.9%, p< 0.000001; 0.48±0.8 vs 0.8±1.2, p=0.03, respectively). When considering the different subset of remission according with its duration, the presence of chronic damage was similarly distributed, without significant difference in the frequency.
Finally at the multivariate analysis, no independent factors resulted associated with remission; conversely, low C3 serum levels seem to be a risk factor for absence of remission (OR=0.15, 95% CI 0.03-0.06).
Conclusions. In the present SLE cohort, a complete remission lasting at least 1 year have been identified in 15% of patients. The remission, regardless of its duration, is associated with a lower chronic damage development, in terms of frequency and severity. This result suggest as a state of remission lasting at least one year significantly improve the SLE patients outcome.

Key words: remissione, duration, chronic damage

S10:06

HOW FREQUENT IS LOW DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS? REAL LIFE DATA FROM A MONOCENTRIC COHORT OF CAUCASIAN PATIENTS

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Objective. To date, there is no generally accepted definition for disease remission in Systemic Lupus Erythematosus, thus, a possible goal in the treat-to-target strategy might be low disease activity, as already adopted in Rheumatoid Arthritis. Lupus Low Disease Activity State (LLDAS) is an expert and literature based definition of minimally acceptable disease activity in SLE patients (1).
The aim of this study is to evaluate what proportion of patients fulfils the definition of LLDAS in a monocentric cohort of Caucasian 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 definition of LLDAS was 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. According with all the items of the definition, the frequency of LLDA was 77.3% (109 pt). No statistical differences were present in organ damage (as expressed by the SLICC/DI score) between patients in LLDA and the others who haven't fulfilled the definition.
Conclusions. In our cohort, a high percentage of patients fulfils the proposed definitions for LLDA. Thus, a minimally acceptable disease activity state is an achievable target in clinical practice. A longitudinal analysis would be necessary to clarify whether patients with stable LLDAS have better clinical outcomes.

Reference
Franklyn K, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2015; 0: 1-7.

Key words: systemic lupus erythematosus, treat to target, low disease activity state

S11: Lupus nephritis: definition and outcomes

S11:04

ANTIPHOSPHOLIPID ANTIBODIES IN LUPUS NEPHRITIS

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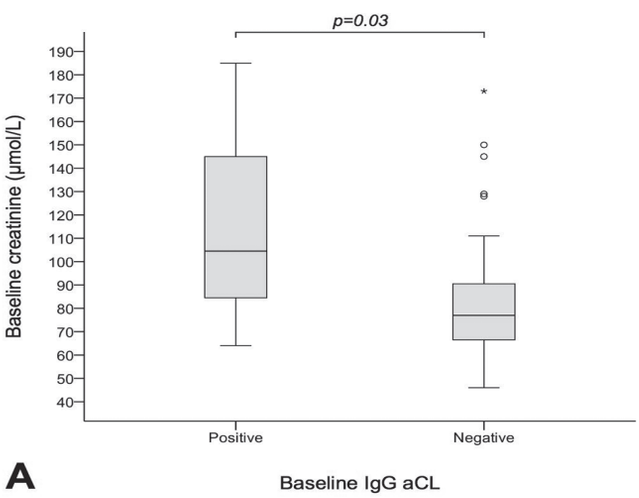
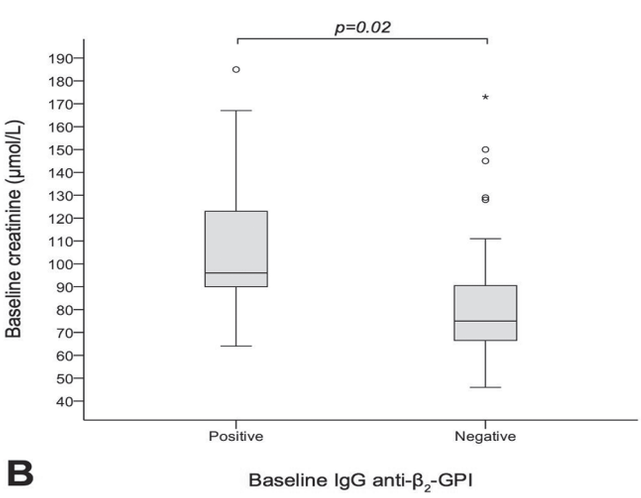
Objective. Lupus nephritis (LN) is a major manifestation of systemic lupus erythematosus (SLE). It remains unclear whether antiphospholipid antibodies (aPL) alter the course of LN. We thus investigated the impact of aPL on short-term and long-term renal outcomes in patients with LN.

Design and Method. We assessed levels of aPL cross-sectionally in SLE patients diagnosed with (n=204) or without (n=294) LN, and prospectively in 64 patients with active biopsy-proven LN (52 proliferative, 12 membranous), before and after induction treatment (short-term outcomes). Clinical responders were defined by at least 50% reduced proteinuria, normal or improved by at least 25% estimated glomerular filtration rate (eGFR), and inactive urinary sediment. Long-term renal outcome in the prospective LN cohort was determined by the eGFR and the Chronic Kidney Disease (CKD) stage, after a median follow-up of 11.3 years (range: 3.3–18.8).

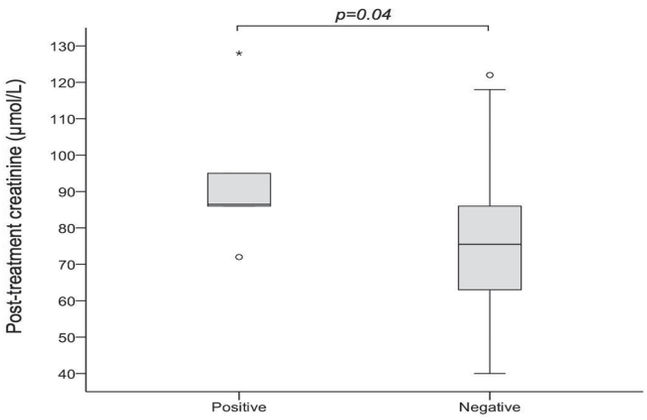
Results. Cross-sectional analysis revealed no association between LN and IgG or IgM anticardiolipin or anti-beta2-glycoprotein I antibodies, or lupus anticoagulant. Both aPL positivity and levels of aPL were similar in patients with active LN and non-renal SLE patients. Following induction treatment for LN, serum IgG and IgM aPL levels decreased in responders ($p<0.005$ for all), but not in non-responders. Both at active LN and after induction treatment, patients with IgG, but not IgM, aPL had higher creatinine levels compared with patients without IgG aPL (Figure). Neither aPL positivity nor levels were associated with changes in eGFR from either baseline or post-treatment through long-term follow-up.



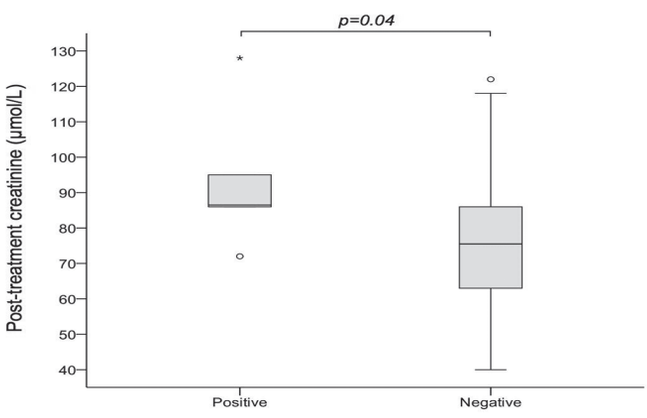
A Baseline IgG aCL



B Baseline IgG anti-β_2-GPI



C Post-treatment IgG aCL



D Post-treatment IgG anti-β_2-GPI

Moreover, aPL positivity and levels both at baseline and post-treatment were similar in patients with a CKD stage of 3 or more and in patients with a CKD stage 1 or 2 at last follow-up.

Conclusions. In conclusion, neither aPL positivity nor levels were found to be associated with the occurrence of LN in patients with SLE. However, IgG aPL positivity in LN patients was associated with a short-term impairment of the renal function while no effect on long-term renal outcome was observed. Furthermore, we noted that IgG and IgM aPL levels decreased following induction treatment in responders, indicating that aPL levels are affected by immunosuppressive drugs.

Key words: systemic lupus erythematosus, lupus nephritis, antiphospholipid antibodies

S11:05

INTERSTITIAL INFLAMMATORY INFILTRATE AT RENAL BIOPSY AND OUTCOMES OF CLASS IV LUPUS NEPHRITIS

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Objective. The role of the extraglomerular kidney interstitial involvement (tubular, peritubular, interstitial) in determining the outcome of lupus nephritis (LN) is still underestimated. The aim of our study is to establish the prognostic impact of interstitial immune infiltrate on the evolution of renal disease in terms of therapeutic response, number of renal flares, renal remission and chronic kidney damage development.
Design and Method. 64 patients with a class IV LN (ISN/RPS classification) have been considered at the onset of renal disease. Active interstitial infiltrate at renal biopsy was considered significant when above 10% of the interstitial surface. Therapeutic response at 6 (T6) and 12 (T12) months follow-up (FU), number of renal flares, persistent renal remission and chronic kidney damage at last FU were evaluated.
Results. Of the 73 LN patients (80.0% female, mean age 41.7±11.6 years, disease duration 8.4±6.8 years), 33 had significant infiltrate (I+) and 31 not (I-). An higher percentage of I+ patients had an active nephritis at T6 than patients without infiltrate (67.9% vs 33.3%; p=0.01), as well as at T12 (52.2% vs 11.5; p=0.002) and at last follow-up (33.3% vs 3.3%; p=0.003). Moreover, I- patients presented higher percentage of early response than I+ patients (70.4% vs 32.1%; p=0.005) and of persistent remission (74.2% vs 28.1%; p<0.01), and lower percentage of renal flare during FU (19.4% vs 59.4%; p=0.01), and of chronic kidney damage (3.2% vs 42.4%; p<0.01).
An early response to therapy (T6) and the absence of significant interstitial infiltrate are the best predictors of persistent remission at multivariate analysis.
Conclusions. The detection of interstitial infiltrate is an important step in defining the prognosis and patients stratification in LN progression.

Key words: lupus nephritis, interstitial infiltrate, renal outcomes

S11:06

ACCELERATED ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS, - A MATTER OF RENAL INVOLVEMENT

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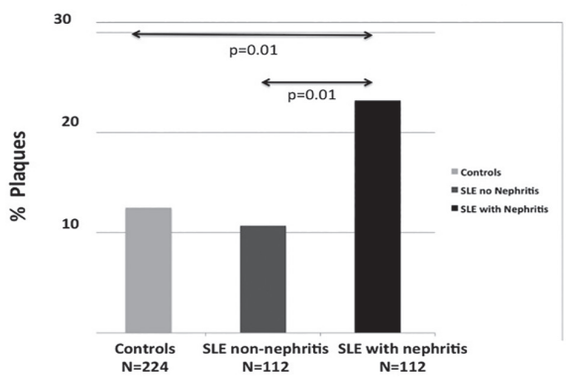
Objective. Atherosclerosis is frequently assumed to be the underlying cause of premature cardiovascular disease (CVD), a major cause of mortality and morbidity, in systemic lupus erythematosus (SLE).
We hypothesized that accelerated atherosclerosis is not a general feature of SLE but prevails in SLE subgroups.

Occurrence of carotid plaques in controls, non-nephritis SLE patients and SLE patients with nephritis.



Design and Method. 281 consecutive SLE patients and 281 population controls, individually matched for age and sex participated. All were investigated clinically, fasting blood samples and risk factor data were collected. We performed B-mode ultrasonography of the carotid arteries and determined plaque occurrence and mean intima media thickness (mIMT). We performed stratified analyses for two subgroups described to be at high CVD risk; 1) patients with nephritis and 2) patients with anti-phospholipid antibodies (aPL), and for one subgroup reported to be at lower CVD risk; 3) patients positive for Sjögrens syndrome antigens A/B (SSA/SSB) antibodies.
Results. Median age was 49(36-59) years, 93% were females. Overall plaque prevalence did not differ significantly (20% vs. 16%), but patients had slightly higher mIMT than controls (0.56 vs. 0.53 mm, p<0.0001). Manifest CVD; ischemic heart, cerebro- and peripheral vascular disease, prevailed in patients (12% vs. 1%, p<0.0001). After age adjustment plaques, but not mIMT, remained associated with CVD. Therefore we focused further analyses on plaques.
Patients with nephritis (40%) had more plaques than their respective controls (23% vs. 11%, p=0.008). While patients positive for aPL (25%) or SSA/SSB antibodies (40%) did not differ form their age matched controls regarding plaque occurrence.
Age was positively associated with plaques (p<0.0001), but the association with nephritis was negative (p=0.02). To overcome the confounding by age a final age-matched nested case-control analysis was performed. The results demonstrate that patients with nephritis had twice as often plaques compared to age-matched non-nephritis patients (p=0.01) and also compared to controls (p=0.01, Fig).
Conclusions. Accelerated atherosclerosis is not a general feature of SLE, but essentially confined to SLE patients with nephritis. High IMT, a more doubtful measure of atherosclerosis, seems to be a more general feature of SLE, but high IMT was not associated with cardiovascular events after adjustment for age. To prevent later cardiovascular events screening for CVD risk factors and vigorous anti-atherosclerotic treatment should be targeted to SLE patients with nephritis and initiated at nephritis onset, which often is at a comparatively young age.

Key words: atherosclerosis, cardiovascular diseases, nephritis

S12: Cell death and lupus

S12:04

INDUCTION OF APOPTOSIS AND AUTOPHAGY IN CIRCULATING PBMC BY MICROPARTICLES FROM PATIENTS WITH SYSTEMIC LUPUS ERYTEMATOSUS

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Objective. Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by heterogeneous clinical manifestation and a complex pathogenesis. Lymphocytes from patients with SLE display multiple alterations, including increased cell activation, abnormal apoptosis and impairment of autophagic pathway. Recently, evidence from genetic, cell biology and animal models suggested that autophagy, a major pathway for organelle and protein turnover, may play a pivotal role in the occurrence and development of SLE. Some studies showed altered profile of circulating microparticles (MPs) in SLE patients. These MPs are released constitutively and may increase as a result of cellular activation and apoptosis. Originally considered as inert debris, MPs are now known to display diverse pro-inflammatory and pro-thrombotic activities, and they are implicated in the intercellular communications. MPs can influence the course of rheumatic and other immune-mediated diseases.
The aim of our study was to evaluate the possible role of MPs purified from SLE patients on the modulation of apoptosis and autophagy in peripheral blood mononuclear cells (PBMCs) isolated from healthy donors.
Design and Method. PBMCs from healthy donors were isolated by Ficoll-Hypaque density-gradient centrifugation, cultured and treated with 0.5,2.5,5 *106 MPs purified by 10 sera of active SLE for 16 h. Apoptosis was measured using FITC- conjugated annexin V (AV) and a propidium iodide (PI) apoptosis detection kit. Acquisition was performed on a FACS Calibur. Autophagy was measured by Western blot for LC3II.
Results. MPs appeared capable of inducing apoptosis. Indeed, PBMCs showed significantly higher apoptosis if treated with MPs compared with untreated cells (percentage of apoptotic cells treated with 5, 2.5 and 0.5*106 MPs: 15, 10, 9 vs. 7%, p=0.0001, p=ns, p=ns, with respectively). Moreover, MPs increased autophagy in a dose response manner (LC3-II/Beta-actin ratio: 1.2, 1, 0,6 vs. 0.5, with 5, 2.5 and 0.5*106 MPs, respectively p=0.0001).β
Conclusions. We demonstrated that MPs from SLE patients induce apoptosis in PBMCs, thereby possibly decreasing the number of circulating leucocytes. The mechanisms underlying such phenomena are not known. Some authors suggested that MPs, through the arachidonic acid pathway, may induce apoptosis. Indeed, this pathway, together with the sphingomyelinic, increase the concentration of ceramide, thus leading into apoptosis mediated by the activation of caspase 8 and by the release of downstream pro-apoptotic factors. Moreover, available data do not exclude the possibility that components of MPs other than arachidonic acid, may also contribute to the ceramide-mediated apoptosis. Finally, this is the first study addressing the relations between MPs and autophagy, suggesting an increase of this cellular event after exposure to MPs. Since an augmented autophagy has been implicated in autoimmunity, it could be of interest to target MPs in order to re-balance the autophagic processes.

Key words: microparticles, autophagy, PBMC

S12:05

DEFECTIVE CLEARANCE OF PHAGOCYTIC SUBSTRATES IN SLE AND OTHER SYSTEMIC AUTOIMMUNE DISEASES REFLECTS INCREASED NETS GENERATION

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Objective. Activated platelets express phosphatidylserine (PS) on their surface. PS is involved in platelet phagocytic clearance, which restricts their hemostatic and inflammatory potential. Activated platelets interacting with adherent neutrophils also induce the Neutrophil Extracellular Traps (NETs) formation via a pathway involving the release of the prototypic alarmin, HMGB1. Little is known on the effects of phagocytosis on the ability of neutrophils to generate NETs, which contribute to the inflammation and tissue injury in diseases in which the phagocytic clearance is jeopardized, including systemic lupus erythematosus (SLE).
Design and Method. The *in vivo* clearance of activated platelets and of apoptotic cells, the platelet activation status, the concentration and characteristic of platelet-derived µparticles (PDµP) and the presence of plasmatic markers of NETs were analyzed in 100 patients with systemic autoimmune diseases or vasculitis, including SLE, systemic sclerosis (SSc), Takayasu arteritis (TA), giant cell arteritis (GCA), rheumatoid arthritis (RA), ANCA associated small vessel vasculitis (AAV). 25 healthy subjects served as controls. The *in vitro* NETs formation induced by PMA or IL-8 and by PDµP of patients and controls in neutrophils that had phagocytosed or not platelets and apoptotic cells was verified using flow cytometry and immunofluorescence. Soluble DNA complexes with myeloperoxidase and with citrullinated H4 histones were assessed by ELISA in the patients plasma and in cell culture supernatants.
Results. Significantly higher fraction of activated platelets and of PDµP expressing the prototypic alarmin, HMGB1 and of NETs byproducts were detected in the blood of patients with SLE, SSc, TA and GCA compared to the blood of healthy controls. In these patients platelets could not be detected in intracellular vesicles of circulating neutrophils. In contrast intracellular platelets were consistently traced in neutrophils of RA patients. *In vitro* experiments indicate that i) neutrophils that had phagocytosed platelets or apoptotic cells do not produce NETs when challenged with bona fide agonists such as PMA or IL-8 and that ii) NETs were elicited by PDµP purified from the blood of patients with systemic autoimmune diseases and vasculitis, but not by PDµP purified from the blood of healthy subjects or RA patients. Blocking experiments indicate that integrity of the HMGB1/RAGE axis is required for the NET generation elicited by patients PDµP.
Conclusions. All together these results indicate that the array of signals associated and released by activated platelets might influence the threshold of NET generation and be involved in the persistence of systemic vascular inflammation.

Key words: neutrophils, apoptosis, microparticles

S12:06

AUTOPHAGY-MEDIATED RELEASE OF TISSUE FACTOR AND IL-17 ON NEUTROPHIL EXTRACELLULAR TRAPS PROMOTES KIDNEY INJURY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. By the use of DNA and miRNA arrays, we have previously shown that patients with active SLE express a strong neutrophil and deregulated autophagy signature. We have also shown that tissue factor (TF), an *in vivo* initiator of the coagulation cascade and a trigger of inflammation, is released on Neutrophil Extracellular Traps (NETs). We sought to investigate their role in lupus nephritis (LN).
Design and Method. Serum and neutrophils from 15 healthy donors and 30 SLE patients (20 active, 5 on treatment with hydroxychloroquine) were isolated. Cultures of ex vivo neutrophils, and *in vitro* stimulation or inhibition studies were performed. Autophagy levels were evaluated by confocal microscopy and immunoblotting. NET release was studied by confocal microscopy. NETs were measured by MPO-DNA complex ELISA in cell culture supernatants and in serum. TF expression was studied by confocal microscopy and immunoblotting. TF activity was measured with thrombin-antithrombin complex ELISA. Kidney biopsies from 10 patients with proliferative LN were examined with immunofluorescence for the presence of TF-decorated NETs and IL-17-decorated NETs.
Results. Neutrophils from patients with active SLE expressed increased autophagy levels and increased NETosis in an autophagy-dependent manner. NETs released from patients with active SLE were decorated with active TF leading to thrombin generation. Serum from patients with active SLE induced autophagy in healthy neutrophils and autophagy-dependent TF-decorated NET release, suggesting that the inflammatory environment of SLE mediates these processes. Treatment of patients with hydroxychloroquine- an autophagy inhibitor- reverses these phenomena. Importantly, TF- and IL-17-decorated NETs infiltrated the kidneys (both in the glomeruli and the tubulointerstitium) of patients with proliferative LN even in the absence of intact neutrophils within the kidney. Ongoing experiments investigate the effects of TF-decorated NETs on renal cell function and morphology.
Conclusions. Neutrophils from patients with active SLE display increased autophagy and undergo increased NETosis in an autophagy-mediated manner that is inhibited by hydroxychoroquine. TF-and IL-17-decorated NETs within the kidneys of patients with proliferative LN may mediate renal injury even in the absence of intact neutrophils. Autophagy-dependent delivery of TF on NETs could provide a link between increased thrombogenicity and inflammation observed in SLE, and may account - in part - for the salutary effects of hydroxychloroquine in LN.

Key words: autophagy, neutrophil extracellular traps, nephritis

S13: B and T cells in lupus

S13:03

IGM ANTIBODIES AGAINST PHOSPHORYLCHOLINE PROMOTE T REGULATORY CELL POLARIZATION IN SLE AND ATHEROSCLEROSIS

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Objective. Phosphorylcholine (PC) is exposed to the immune system in microorganisms, especially parasites and nematodes and oxidized LDL among others. Atherosclerosis and cardiovascular disease (CVD) are increased in SLE. We reported that IgM anti-PC is negatively associated with atherosclerosis and cardiovascular disease (CVD) in the general population but also has protective properties in SLE. IgM anti-PC is anti-inflammatory, increases clearance of apoptotic cells and decreases uptake of oxLDL in macrophages. An increased proportion of Th17 but decreased of T regulatory (Tregs) cells have been described in SLE which could contribute to the disease, and is also implicated in atherosclerosis. Here we study effects of IgM anti-PC on Th17 and Tregs from healthy controls, SLE-patients and from atherosclerotic plaques.
Design and Method. Mononuclear leukocytes were isolated from peripheral blood obtained from healthy blood donors, from SLE patients with age- and sex-matched controls and from atherosclerotic plaques. The proportion of Th17 ($CD4^+CCR6^+$) and Treg ($CD4^+CD25^+CD127$ dim/-) cells in $CD4^+$T cells from SLE patients and health donors. CCR6, CD25 and CD127 expression were determined by flow cytometry analysis in $CD4^+$T cells after 6 days culture with Th17 or Treg-polarizing cytokines, with PMA and Ionomycin stimulation. IgM Anti-PC were extracted from total IgM, with flow through IgM used as controls. The antibodies were added one day before harvest.
Results. After addition of IgM anti-PC, the proportion of T regs increased significantly and dose-dependently, with maximal effect at 5µg/mL among healthy donors. IgM control antibodies had no effect on T cells. Then we investigated six SLE patients with matched controls. In untreated cells, SLE patients had a significantly lower proportion of T regs and higher proportion of Th17 cells. After addition of IgM anti-PC, the proportion of T regs increased significantly in both groups, where T regs from SLE patients reached similar levels as controls and was thus normalized. IgM anti-PC significantly reduced production of IL-17 and TNF-alpha in supernatants from cell culture. Similar data was obtained from atherosclerotic plaques. Control antibodies had no effect. IgM anti-PC or control antibodies had no effect on Th17 cells in these experiments.
Conclusions. IgM anti-PC promotes T reg polarization in SLE and atherosclerosis and could have protective properties, with therapeutic implications.

Key words: antibodies, phosphorylcholine, T regulatory cells

S13:04

IL-10 PRODUCING CCR6+T-CELLS ARE A DISTINCT POPULATION OF B-HELPER T-CELLS THAT PLAY A PATHOGENIC ROLE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Interleukin-10 (IL-10) is a controversial cytokine since it is able from one side to inhibit myeloid cells from producing pro-inflammatory cytokines and up-regulating MHC and co-stimulatory molecules, thus inhibiting T cell responses; on the other side, IL-10 is a potent B-cell growth and differentiation factor, that promotes survival, proliferation, isotype switching and differentiation of human B-cells.
In Systemic Lupus Erythematosus (SLE) IL-10 plays a pathogenic role because it promotes auto-reactive B-cell response, although the identity of pathogenic cells which are the source of IL-10 is still illusive.
Here we characterize a population of IL-10 producing T cells that express CD127 and CCR6 and help B cell responses, suggesting that these cells play a pathogenic role in SLE.
Design and Method. We first identified CCR6+CD127+ cells in human tonsils from healthy donors, and test their capacity to provide B cell help by analyzing total IgG secretion by B cells. We then compared them with Th17 cells, which also express CCR6, Tfh cells, which also provide B cell help, and Tr1 cells, which also produce IL-10.
We than tested the presence of CCR6+CD127+ cells in the spleen of IL-10 reporter mice, and their capacity to provide B cell help *in vivo*. Finally, we checked the presence of CCR6+CD127+ in patients with active SLE and their pathogenic potential through total IgG and autoantibodies production by B cells.
Results. We found that IL-10 producing CCR6+CD127+ cells are present in human tonsils and provide B cell help. Despite their characteristics, they are different from Th17, from Tr1 and from Tfh, thus representing a distinct B helper T cell population.
In mice, these cells are present in the spleen, and provide *in vivo* B cell help in a partially IL-10 dependent manner.
In SLE patients, CCR6+CD127+ cells are accumulated and contribute to the systemic IL-10 and autoantibody production, thus promoting disease progression.
Conclusions. In conclusion, we identified a novel population of B-helper T-cells that is liekly to play a prominent pathogenic role in SLE. The monitoring of these cells might thus be a prognostic marker of SLE progression and/or activity, and targeting their B-helper functions is a promising therapeutic strategy.

Key words: CCR6, pathogenic T cells, autoantibodies

S13:05

BANK1 INTERACTS WITH TRAF6 AND MYD88 IN INNATE IMMUNE SIGNALING OF B CELLS

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Objective. The present study aimed to investigate the role of the lupus-associated risk gene BANK1 in innate immune signaling in B cells focusing on its interaction and function with two of the key mediators in interferon and cytokine production, TRAF6 and MyD88.
Design and Method. Confocal microscopy was performed in HEK293-transfected cells with fluorescent-tagged proteins and immunofluorescence reactions in Namalwa B cells, respectively to study the subcellular localization of proteins. In parallel, co-immunoprecipitation reactions were performed to study protein-protein interactions of BANK1 with proteins involved in Myddosome complex formation. Mutagenesis analyses were conducted on putative TRAF6 binding sites in BANK1 with subsequent co-immunoprecipitations to demonstrate significance of each binding site for protein-protein interaction. And ubiquitination assays on TRAF6 were applied to determine any functional influence of BANK1 on the ubiquitination status of TRAF6 which is important to activate innate immune signaling.
Results. We have identified four putative consensus-binding motifs TRAF6 (Pro-X-Glu-X-X-(aromatic/acidic residue) in the BANK1 protein suggesting a functional involvement. Confocal microscopy showed co-localization of BANK1 and TRAF6 and also with MyD88. Immunofluorescence analyses in B cells confirmed this co-localization. Additionally, BANK1 and TRAF6 co-localized also with TLR7 and TLR9 after immunofluorescence in purified splenic mouse B cells.
Protein-protein interaction analyses revealed a physical interaction of BANK1 with TRAF6 and also with MyD88 in transfected HEK293 cells. We also determined that endogenous proteins of BANK1 and TRAF6 interact upon stimulation with the TLR7 agonist imiquimod in the Namalwa B cell line. Point mutation of the tyrosine in one of the 4 putative TRAF6 binding sites of BANK1 abrogated binding indicating that protein interaction is mediated by this motif. Ubiquitination assays revealed that BANK1 regulates TRAF6 lysine-63 autobiquitination which signals for TRAF6 activation and consequently interferon and cytokine production.
Conclusions. Our study is the first to provide new insights on (i) a role of BANK1 in MyD88-TRAF6 signaling upon endosomal Toll-like receptor stimulation, (ii), the regulation of TRAF6 autoubiquitination by BANK1, and (iii) the understanding of cellular and molecular mechanisms that can be involved in lupus development.

Key words: BANK1, Toll-like receptor signaling, B cells

S13:06

IN VITRO INDUCED REGULATORY T-CELLS CAN REDUCE SEVERITY OF LUPUS ARTHRITIS

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Objective. We herein investigate if *in vitro* induced regulatory T-cells (iTreg) are capable of ameliorating Pristane-induced lupus (PIL) arthritis and help us evaluate possible new treatment options.
Design and Method. BALB/c mice were injected i.p. with either 0.5ml of pristane (PIL-group) or PBS (controls). Naive $CD4^+$ thymocytes were sorted and cultured and cell suspensions with >80% of $CD4^+FoxP3^+$ cells (iTreg) were injected intravenously (i) once when PIL was induced (5x106 iTreg, iTreg-boost), or (ii) every 4 weeks (1x106 iTreg, iTreg-rep). Animals were monitored for paw swelling and grip strength. After 8 months histological analysis evaluated for cartilage degradation, number of osteoclasts and the extent of inflammation and bone erosion. In addition, the cellular composition of the inflammatory tissue was determined by a cell-identification algorithm for nuclear segmentation (HistoQuest). Serum levels of anti-dsDNA, anti-histone and anti-chromatin antibodies were measured by ELISA.
Results. Monthly injections of 1x106 iTreg reduced the clinical as well as the histological severity of PIL-arthritis, seen by a higher mean grip strength, less mean paw swelling and retardation of the symptom onset. 62% of PIL-mice and 33% of iTreg-rep mice had erosive arthritis. There was a significant reduction of arthritis severity in all histological parameters. The single boost of 5x106 iTreg could not prevent joint manifestation. However, a slight retardation in 'loss of grip strength' and a significantly less erosive area was seen. In regards to the cellular composition of the inflammatory tissue, a significantly increased relative amount of Foxp3 cells was seen in the iTreg-rep group compared to the PIL group (5.2±2.3 vs. 0.6±0.2). Corresponding to the reduced severity in joint involvement, the iTreg-group had significantly lower serum levels of antibodies.
Conclusions. Repeated injections of iTreg ameliorate the clinical and histological severity of PIL- arthritis. A single boost of iTreg at the time of disease induction does not prevent joint manifestation, but retards the onset of symptoms and progression of erosive bone degradation. Thus, iTreg have significant positive effects on PIL arthritis, which may have consequence for future therapeutic considerations.

Key words: regulatory T-cells, pristane induced lupus, arthritis

S14: Damage and comorbidities

S14:03

COMORBIDITIES IN SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To determine the prevalence and spectrum of comorbidities in a predominantly Black cohort of systemic lupus erythematosus (SLE) patients at a tertiary hospital in South Africa.
Design and Method. A retrospective record review of 200 randomly selected SLE patients attending the Lupus Clinic, Chris Hani Baragwanath Hospital, Soweto as at 31 May 2015. Patients met the 1997 ACR classification criteria for SLE, were >16 yrs at diagnosis and followed-up for at least 6 months. Data abstracted included demographics, clinical features, autoantibody results and comorbidities, including, but not restricted to those listed in the Charlson Comorbidity Index (CCI). Disease duration was defined as time from diagnosis of SLE by an internist or rheumatologist. Serious infections were defined as those requiring hospitalisation and intravenous antibiotics.
Results. Most patients were black African females (94%) with a mean (SD) age of 34.6 (11) yrs and median (IQ range) disease duration of 7 (3.25-12) yrs. The most frequent clinical features (%) were arthritis/arthralgia (74), discoid lupus erythematosus (45.4), and and nephritis (43). Most patients (99.5%) were ANA positive and 80% showed other immunological evidence of SLE. Baseline and cumulative prevalence of 1 or more comorbidities were 36.5% and 56.0%, respectively and the mean CCI was 1. Some of the important comorbidities are shown in the Table below.
Independent predictors of hypertension were age at onset, disease duration, renal and central nervous system involvement. Predictors of infection were the presence of anti-sm antibodies, number of ACR criteria met, thrombocytopaenia and use of mycofenolate mofetil. The use of azathioprine and disease duration were predictors for tuberculosis (TB).

Comorbidity	Frequency n (%)	Comorbidity	Frequency n (%)
Hypertension	87 (43.5)	Tuberculosis	30 (15)
Severe infection	58 (29)	HIV infection	19 (9.5)
Peptic ulcer disease	17 (8.5)	Myocardial infarction	3 (1.5)

Conclusions. There is a high burden of comorbidities in South African patients with SLE. Hypertension, severe infections, TB, HIV infection and peptic ulcer disease were the commonest comorbodities with an association to disease duration and use of immunosuppressive agents. Conversely, cardiovascular complications, a major comorbidity reported in American and European studies, were rare, despite a high prevalence of hypertension. This study highlights the importance of close clinical monitoring of South African SLE patients for severe infections, in particular TB and HIV.

Key words: comorbidities, Africa, SLE

S14:04

RISK OF ORGAN DAMAGE AND MORTALITY IN SLE PATIENTS FULFILLING THE ACR OR THE SLICC CLASSIFICATION CRITERIA: A 10-YEAR, PROSPECTIVE INCEPTION COHORT STUDY

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Objective. The new SLICC classification criteria for SLE allow inclusion in clinical trials of patients previously regarded as 'incomplete' lupus. However, it is not known whether use of the SLICC criteria leads to recruitment of a study population with milder prognosis.
Aim of this study is to compare organ damage and mortality from inception up to 10 years after diagnosis between SLE patients classified at baseline with the ACR criteria and those fulfilling only the new SLICC classification criteria.
Design and Method. Prospective study of an inception cohort of SLE patients enrolled from 2002 at a tertiary care lupus clinic. Patients fulfilling the ACR-

revised and/or the SLICC classification criteria for SLE at inception were included. Damage was defined as a score>=1 in the SLICC Damage Index (SDI). Patients were grouped according to the inception SLE classification status (ACR versus only SLICC criteria) and compared using Mann-Whitney U or Chi-square tests, as appropriate. Multivariate Cox regression was used to identify independent predictors of (i) SDI>=1 and (ii) death. We compared the 10-year study outcomes according to the SLE classification status at inception, after adjusting for the potential baseline confounders: gender, age at diagnosis, lupus nephritis, neurolupus, SLEDAI-2k score, prednisone daily dosage, any antiphospholipid antibody, lupus anticoagulant, anti-dsDNA antibodies, anti-Sm antibodies, hypertension and ever smoking. Were considered as statistically significant p values<0.05.
Results. We included 192 patients (82.8% female, mean age at diagnosis =37.7±15.4 years, 69.8% fulfilling the ACR criteria and 30.2% only the SLICC criteria at inception). At baseline, patients fulfilling the ACR criteria presented a higher median SLEDAI-2k score (p<0.0001), a higher proportion had lupus nephritis (p<0.01) and previous smoking habits (p<0.05), but had lower prevalence of antiphospholipid antibodies (p<0.001) and lupus anticoagulant (p<0.001), in comparison with those fulfilling only the SLICC criteria. More patients with ACR criteria received prednisone at inception (p<0.001). There were no significant differences between groups regarding the other baseline covariates.
During follow-up, 24.0% of patients developed organ damage and 4.2% died. At time of last visit, patients presented a median SLEDAI-2k score=2, without difference between inception classification groups. Patients fulfilling the ACR criteria more frequently received immunosuppressants (p<0.01) and prednisone (p<0.0001). Hydroxychloroquine was given to 95.8% of patients, without difference between groups.
The Cox regression models showed no significant differences in risk for damage [(HR 95% CI) 0.991 (0.453-2.167)] or death [(HR 95% CI) 0.694 (0.107-4.506)] between the two groups. Age at inception was a significant predictor for damage (p<0.05) and death (p<0.01). Neurolupus was predictive of damage (p<0.0001). No significant effect was found with other covariates.
Conclusions. There were no differences in major outcomes of organ damage and mortality up to 10-year follow-up of SLE patients fulfilling, at inception, either the ACR criteria or only the SLICC classification criteria.

Key words: classification criteria, organ damage, survival

S14:05

IMPACT OF HIV INFECTION ON THE COURSE OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. To determine the impact of HIV infection on rate and reasons for hospital admission in SLE patients.
Design and Method. A restrospective nested case-control study, comparing SLE with HIV infection ('HIV group') to a SLE group without infection ('Control group'), matched for age, duration of follow up and lupus nephritis. Data abstracted from the case records included.
Results. Of the 674 records of SLE patients reviewed, 40 of 543 patients tested were found to be HIV positive (7.4 %), 5 had false positive HIV serology, 496 were known HIV negative. The majority of patients were female (97.5%). The mean (SD) age at SLE diagnosis and HIV diagnosis were respectively 32.6(11.5) and 36.0 years (10.6). 14 patients were HIV positive at the time of SLE diagnosis. The mean (SD) duration of follow up ,was 8.9 years (6.3). In terms of SLICC criteria 38(95%) of HIV positive patients with SLE were ANA positive and 15(37.5%) had nephritis. 4 patients had hospital reported death. 81 admissions were recorded. The rate of admission per 100 patient years was 62 (162). Infections and SLE flares being the reasons for admissions in 45.7% and 33.3% respectively.
There was no significant difference in the overall rate of admission between admissions post HIV infection and admissions in the control group, the p value was 0.838. However, the rate of admissions for SLE Flare was lower in admissions after HIV infection, p value 0.002 and higher for admission for Infection, p value 0.0074
Conclusions. HIV infection at Chris Hani Baragwanath hospital is associated with substantial morbidity and mortality. SLE is not uncommonly associated with false positive ELISA tests. The admission rate for SLE Flare is lower post HIV infection.

Key words: lupus, HIV, Africa

S14:06

VASCULAR AGE, CALCULATED BY PULSE WAVE VELOCITY, IS GREATER THAN CHRONOLOGICAL AGE IN PATIENTS WITH SYSTEMIC LUPUS ERITHEMATOSUS: A MONOCENTRIC CROSS-SECTIONAL STUDY

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Objective. Systemic lupus erythematosus (SLE) patients are at increased risk of cardiovascular events, which is disproportionate as compared to traditional cardiovascular risk profile assessment. The use of non-invasive biomarkers of vascular damage might be helpful for a more accurate stratification of cardiovascular risk in these patients. Aim of the study is to evaluate determinants of early vascular aging in patients with SLE.
Design and Method. SLE patients fulfilling the 1997 ACR classification criteria and regularly followed at our lupus clinic were selected from our prospective cohort. At the time of enrollment, medical and pharmacological history were collected. Disease activity and organ damage were evaluated according to the SELENA-SLEDAI and the SLICC/ACR-DI scores, respectively. Carotid-femoral pulse Wave Velocity (PWV) and Augmentation Index (AI) were acquired by applanation tonometry. Vascular age was derived as the age for which measured PWV corresponds to the 50th percentile of the International Reference Values, stratified for blood pressure.
Results. 70 patients with SLE (97%female) with a mean disease duration of 14±10 years (9-24) years were enrolled from our outpatients clinic. Mean chronological age was 42±11 years, 32% were hypertensive, 40% were overweight (mean BMI 22± (19-25) kg/mq) and 25% had a diagnosis of dyslipidemia. As expected, disease activity was generally low with a mean SLEDAI score of 2.5±3.2 (range 0-16) while at least one item of damage was present in 60% of patients (mean SLICC/ACR-DI 1.0±1.6). PWV was 8.2±1.8 m/s, for a corresponding vascular age of 48±13 years (p<0.001 vs chronological age) and an excess age of +6.0±12.9 years.
Excess age was greater in the presence of hypocomplementemia (+ 8 vs -6 years, p=0.01), renal involvement (+12 vs +2, p=0.002) and previous therapy with cyclophosphamide (p=0.04). Interestingly, pre-menopausal patients had also higher vascular age (+9 vs +1 m/s, p=0.04).
Conclusions. In this cohort of outpatients SLE, vascular age is significantly greater than chronological age. Early vascular aging, detected as excess vascular age estimated by PWV, is associated with a more severe disease profile and is greater in younger, pre-menopausal women. Disease activity, duration and organ damage in district different by the kidneys are not related with excess vascular age.

Key words: systemic lupus erythematosus, vascular age, pulse wave velocity

S15: Targeting B cells and plasma cells in SLE

S15:03

PROTEASOME INHIBITION WITH BORTEZOMIB IN SLE PROMOTES THERAPEUTICALLY RELEVANT DEPLETION OF SHORT- AND LONG-LIVED PLASMA CELLS BUT DOES NOT PREVENT THEIR REGENERATION

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Objective. Long-lived plasma cells (PCs) are an essential component of the pathogenic immunologic memory that are resistant to immunosuppressive and B cell depleting. We recently demonstrated that their targeting with the proteasome inhibitor bortezomib resulted in therapeutically relevant plasma cell depletion in refractory cases of SLE. Here we investigated in detail the cellular and serologic responses of bortezomib treatment in SLE patients.
Design and Method. Eight patients received a median of two 21-day cycles of intravenous bortezomib 1.3mg/m2 as induction therapy for active SLE. Disease activity was assessed using the SLEDAI-2K score. Serum concentrations of anti-double-stranded DNA (anti-dsDNA) and BAFF levels were monitored. Flow cytometry was performed to analyse peripheral blood B cells, T cells and PCs and Siglec-1 expression on monocytes as surrogate marker for type-I interferon (IFN).
Results. Upon proteasome inhibition, serum anti-double-stranded (ds)DNA and anti-nucleosome levels significantly declined and complement levels and serum BAFF levels significantly increased. While number and phenotype of peripheral blood T- and B cells remained unaffected, proteasome inhibition was associated with a significant depletion of HLA-DR+ (p=0.024) and HLA-DR- (p=0.038) peripheral blood and bone marrow PCs (by ~50%), but a rapid repopulation of autoreactive plasma cells was observed after withdrawal of bortezomib. Siglec-1 expression on monocytes significantly declined.
Conclusions. These findings identify proteasome inhibitors as a promising novel treatment option for patients with refractory SLE by targeting short- and long-lived PCs and type I IFN activity. Bortezomib efficiently induces short-term remissions but requires maintenance treatment to inhibit PC regeneration from their precursor B cells for sustained efficacy.

Key words: plasma cells, proteasome inhibition, lupus

S15:04

GLYCOGEN SYNTHASE KINASE-3 IS HYPERPHOSPHORYLATED IN SLE AND PROVIDES A FEEDBACK MECHANISM FOR THE GENERATION OF REGULATORY B CELLS

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Objective. Glycogen synthase kinase-3 (GSK3) is a constitutively active serine-threonine kinase, which integrates upstream signals from a number of cell growth and inflammation associated pathways, such as MAPK and Akt-mTOR1. In response, GSK3 becomes phosphorylated and loses its kinase activity for glycogen synthase and numerous other substrates, modulating, notably WNT/β-catenin, NF-κB, and STAT1/3 signalling. The diversity of these targets places GSK3 in a central role in regulation of the immune response.
The role GSK3 may play in systemic autoimmune disease is poorly understood. We sought to further understand its biology and function in SLE and B cell homeostasis.
Design and Method. Using phospho-specific antibodies to GSK3 and key components of the GSK3 pathway, Akt and β-catenin, we performed a case-control study using intracellular flow cytometry and Luminex techniques to analyse its activity in the B cells of SLE patients and healthy controls. Murine B cells were negatively isolated for further study of GSK3 signalling.
Results. GSK3 is differentially phosphorylated in the B cells of patients with SLE, leading to an elevation in the level of one of its key target proteins β-catenin. Stimulation of murine B cells revealed that TLR9 ligation was a potent inducer of GSK3 phosphorylation. Treatment of B cells using the highly selective inhibitor CHIR99021, which mimics GSK3 phosphorylation, lead to a substantial increase in the number of IL-10 producing regulatory B cells following stimulation with CpG or anti-IgM. In turn, regulatory B cells generated from an IL10-GFP transgenic mouse had significantly increased GSK3 phosphorylation than IL-10 negative B cells.
Conclusions. We hypothesize that GSK3 is phosphorylated in B cells in response to TLR activation, and that this process then favours the generation of Bregs as a regulatory feedback mechanism to limit further inflammation. Mechanistically, we further hypothesize that β-catenin, modulated by GSK3, may be important in this process, as an IL-10 producing tolerogenic dendritic cell phenotype has previously been shown to be dependent on -catenin, a key GSK3 substrate. Pharmacological GSK3 inhibitors have been developed and used in up to phase II clinical trials for neurodegenerative disease, with an acceptable safety profile.
The favourable properties of GSK3 inhibition therefore suggests the possibility of rapid clinical translation for the treatment of human autoimmune disease.

Key words: glycogen synthase kinase, regulatory B cells

S15:05

SUPPORT FOR PHOSPHOINOSITOL 3 KINASE INHIBITORS AS TREATMENT OF LUPUS USING IN SILICO DRUG REPURPOSING ANALYSIS

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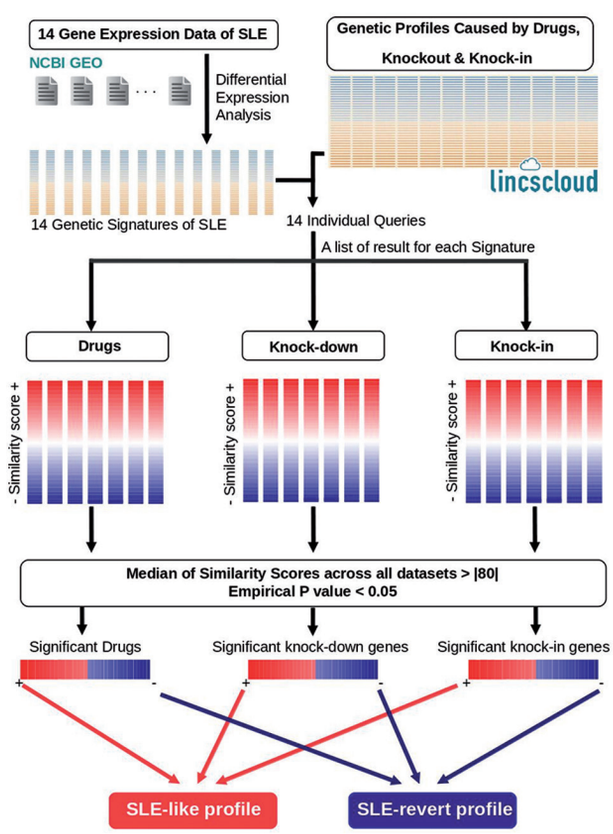
Objective. Systemic Lupus Erythematosus is a clinically heterogeneous and at times life-threatening disease with few treatment options and difficult diagnosis. Current treatments are not fully effective and show highly variable responses. In this regard, large efforts have focused in developing new classification schemes of the disease and more effective therapeutic strategies. Drug repurposing based on the comparison of gene expression signatures has been an effective technique for the identification of new therapeutic approaches. Here we present a systematic drug repurposing analysis based on gene expression signatures derived from blood cells of SLE patients to discover potential new drug candidates and target genes.



Design and Method. we collected and processed a compendium of gene expression data sets of SLE from the NCBI Gene Expression Omnibus database and derived a set of gene expression signatures of different blood cell types from SLE patients calculated using R environment. With these signatures, we queried the Lincscloud database independently, which contains tens of thousands of drug and genetic perturbation-caused profiles. We obtained a list of drugs, knock-in and knock-down genes for each query. Then, we calculated the median of the similarity scores of each drug, knock-down and knock-in genes across all lists of results of SLE-signatures queried and we estimated an empirical p-value. Finally, we selected only the significant results showing a median similarity score higher than 80, in absolute value
Results. We obtained a list of genes as potential targets, with their associated biological pathways and a list of drugs that shows inverse correlation with the genetic signature of SLE.
Conclusions. Our results suggest that phosphoinositol 3 kinase inhibitors affecting biological pathways impaired in SLE are the best potential therapeutic option.

Key words: drug-repurposing analysis, lupus, lincscloud

S15:06

THE INCREASE OF CIRCULATING CD4+ T-CELLS WITH EFFECTOR PHENOTYPE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS MAY BE REVERTED AFTER BELIMUMAB THERAPY

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Objective. T-cell activation may be one of the pathogenic mechanisms of systemic lupus erythematosus (SLE). After repeated antigenic stimulation, T-cells undergo different modifications, leading to the differentiation into effector memory T-cells (CCR7-CD45RA-) and highly experienced memory T-cells (CCR7-CD45RA+). Similarly, down-modulation of CD28 may lead to the expansion of the CD28-T-cells, a subpopulation with peculiar effector activities.
Recent studies showed that memory CD4+ T-cells are increased in the peripheral blood of SLE patients, whereas contradictory data are reported on CD28-T-cells. Belimumab is an anti-Blys therapy approved for SLE.
The aims of this study were the characterization of T-cell phenotype in a cohort of patients with SLE, according with disease activity, and the analysis of T-cell phenotype modifications after 6 months of therapy with belimumab.
Design and Method. Phenotypic analysis of peripheral blood T lymphocytes was made by flow-cytometry. First, a cross-sectional study on 41 consecutive SLE patients was performed. Second, 7 patients treated with belimumab were longitudinally followed. Disease activity was evaluated by SLEDAI-2K score.
Results. SLE patients were divided in two groups according disease activity: patients with SLEDAI-2K > or = 6 (n.6) had a higher percentage of circulating CD4+T-cells with CD28- phenotype (11 vs 2.5%, p=0.01), as well as of those with an effector memory (34 vs 18%, p=0.03), or highly experienced memory (8 vs 1 %, p=0.01) phenotype, in comparison with patients with low disease activity (n.35).
After 6 months of treatment with belimumab, a trend toward a reduction of the $CD4^+CD28^-$ T-cells was observed (from 10.5% to 4.6%; p:0.12). In particular, a reduction of $CD4^+CD28^-$ T-cells showing an effector memory phenotype (from 31.6 to 26 % of $CD4^+CD28^-$ cells, p=0.01) was found.
Conclusions. $CD4^+$ T-cells subpopulations displaying phenotype characteristics of effector lymphocytes are proportionally expanded in patients with active SLE, but some of these abnormalities seems to be reverted by anti-BlyS therapy.
Since the presence of BlyS receptor 3 on T cells and of a BLyS-dependent T-cell activation pathway have been well demonstrated, further studies are warranted to understand the possible effects of anti-BlyS therapy on T cells from SLE patients.

Key words: T lymphocytes, belimumab, systemic lupus erythematosus

S16: SLE registries and cohorts (1)

S16:03

BASELINE CHARACTERISTICS AND RISK FACTORS OF SLE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION: A MULTI-CENTER STUDY IN CHINA

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Objective. Chinese SLE treatment and Research Group (CSTAR) started a multicenter retrospective cross-sectional study recruiting SLE patients with pulmonary arterial hypertension (PAH) since 2006. This study aims to investigate the baseline characteristics and risk factors of SLE-associated PAH in Chinese patients.

Table 1.Baseline characteristics of patient with SLE associated PAH

Charactieristics	SLE-aPAH (n=292)
Female sex	99.3% (290/292)
Age at recruitment, yr	35.3±10.3
PAH duration, yr	1.5±2.1
WHO Fc I-II	44.9% (131/253)
6MWD, m	407.3±97.9
BNP, ng/L	627.5±1371.7
NT-proBNP, pg/ml	1678.3±2302.7
RHC	
mPAP, mmHg	46.2±12.0
PAWP, mmHg	7.84±3.92
PVR, WU	10.86±5.57
CI, L/min×m^2	2.77±0.91
UCG	
PASP, mmHg	77.30±20.85
RV diameter, mm	38.3±9.9
Treatment regimen	
Glucocorticoid	99.3% (290/292)
Immunosuppressants	78.8% (230/252)
Cyclophosphamide	58.2% (170/248)
≥2	41.4% (121/291)
Medications for PAH	70.2% (205/292)
ERA	37.7% (110/292)
PDE-I	41.1% (120/292)
PG	4.8% (14/292)
≥2	13.0% (38/292)

6MWD=6 minutes walking distance, BNP=brain natriuretic peptide, CI=cardiac index, ERA=endothelin receptor antagonist, mPAP=mean pulmonary arterial pressure, NT-proBNP=N-terminal prohormone of brain natriuretic peptide, PASP=pulmonary arterial systolic pressure, PAWP=pulmonary arterial wedge pressure, PDE-I=phosphodiesterase inhibitor, PG=prostaglandin analogs, PVR= pulmonary vascular resistance, RHC=right heart catheterization, RV=right ventricular, UCG=echocardiography, WHO Fc=WHO functional class.

Table 2.Independent risk factors identified by multivariate logistic regression analysis

	P	OR	95% CI	
Interstitial lung disease	<0.001**	3.407	2.117	5.483
Serositis	<0.001**	5.642	3.646	8.730
SLEDAI	<0.001**	0.890	0.860	0.920
Anti-RNP	<0.001**	12.791	9.070	18.040
DLCO/Pred<70%	<0.001**	8.335	5.464	12.713

DLCO=diffusing capacity for carbon monoxide of the lung
*P<0.05, **P<0.01

Design and Method. This study involves thirteen high ranked rheumatology centers in China. All SLE patients were fulfilled the 1997 revised ACR criteria. PAH was diagnosed based on ESC/ERS guidelines by right heart catheterization. Cross sectional analysis from time of enrollment was conducted to describe the demographic features, clinical manifestations, laboratory findings and medications.

Results. Up to 2016, 292 SLE-associated PAH were enrolled in this study. 99.3% were female, mean age was 35.3±10.3 years. The mean duration between PAH symptom onset to diagnostic catheterization was 1.5±2.1 years. 99.3% and 70.2% patients were treated with immunosuppressants and PAH-targeted therapies respectively. 1986 SLE patients without PAH registered in CSTAR database during the same time period were enrolled as control group. Interstitial lung disease (OR 3.407, 95%CI 2.117-5.483, p<0.001), serositis (OR 5.642, 95%CI 3.646-8.730, p<0.001), anti-RNP (OR 12.791, 95%CI 9.070-18.040, p<0.001) and DLCO/Pred<70% (OR 8.335, 95%CI 5.464-12.713, p<0.001) were independent risk factors of PAH in SLE patients by logistic regression. SLEDAI (OR 0.890, 95%CI 0.860-0.920, p<0.001) was negatively related to SLE-associated PAH.
Conclusions. This study is so far the largest multi-center cohort worldwide of patients with SLE associated PAH confirmed by a RHC-based diagnostic algorithm. Interstitial lung disease, serositis, anti-RNP antibodies and DLCO/Pred<70% are suggested as independent risk factors of PAH in SLE patients.

Key words: pulmonary hypertension, multi-center study, risk factors

S16:04

ADULT OUTCOMES IN A LARGE COHORT OF CHILDHOOD-ONSET SLE PATIENTS: FERTILITY AND PREGNANCIES – THE CHILL-NL STUDY

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Objective. Childhood-onset systemic lupus erythematosus (cSLE) is a lifelong autoimmune disease involving multiple organ systems. Information regarding long term outcomes such as fertility and pregnancies is scarce for this population. In this large cohort of 111 adult cSLE patients, we describe the effects of the disease on family planning, fertility and pregnancies. The outcomes were compared to 40 SLE patients and to the Dutch norm population when relevant.

Table 1: Disease characteristics and pregnancy characteristics	cSLE: n=101	SLE n=37
Ethnicity		
White	71%	68%
Non White (%)	29%	32%
Age at diagnosis in years *(median (range))*	14 (5 – 17)	26 (18 – 63)
Disease duration in years *(median (range))*	20 (1 – 55)	11 (1 – 34)
Age at study visit *(median (range))*	34 (18 – 65)	38 (25 – 76)
Current SLEDAI-2K score *(median (range))*	4 (1 – 14)	5 (0 – 10)
SDI-score *(median (range))*	1 (0 – 8)	1 (0 – 7)
Patients with SLICC-DI ≥ 1	61%	57%
Limited in sexuality due to disease	27% (27/99)	24% (8/35)
cSLE as restrictive factor in pregnancy wish	33% (33/99)	34% (12/35)
Patients ever pregnant (after diagnosis of SLE)	37% (37/101)	42% (10/24)
With a history of cyclophosphamide use	22% (8/36)	20% (2/10)
Time to first pregnancy in months *(median(range))*	2 (0 – 84)	1 (0 – 12)
Total number of pregnancies	87	20
Miscarriages	14% (12/87)	25% (5/20)
Abortion	6% (5/87)	0
Any complication during pregnancy > 20 weeks gestation	44% (31/70)	5% (1/20)
Stillbirth/fetal death	6% (4/70)	0
Pregnancy induced hypertension	6% (4/70)	0
Pre-eclampsia/HELLP	10% (7/70)	0
Premature birth	7% (5/70)	5% (1/20)
Placental abruption	5% (4/70)	0
Other	9% (6/70)	0

Methods. Adults with cSLE were referred to the CHILL-NL (CHILdhood Lupus-NetherLands) study team via Dutch medical specialists and patient organizations. All patients were seen for a single study visit. Information regarding fertility and pregnancies were assessed by structured questionnaires and checked with medical records. A control group of SLE patients was included in the study. Data of both patient groups were compared to data of the Dutch female population when applicable.

Results. We studied a cohort of 101 female cSLE patients with median age at diagnosis of 14 years (range 5–17) and median disease duration of 20 years (range 1–55). 27% of patients felt that effects of cSLE limited them in their sexuality. One third of the patients felt that the disease was a restrictive factor in wanting children. They feared complications during pregnancy (53%), complications during labour (31%), and problems with raising children (36%). 30% of patients feared their children would be diagnosed with SLE.
Thirty-seven cSLE patients (37%) reported to have been pregnant at least once. Eight of them (22%) had a history of cyclophosphamide use. Time to pregnancy was less than 12 months in all but one patient. A total of 87 pregnancies were reported and resulted in 66 live births (76%), 12 miscarriages (14%, comparable to the miscarriage rate of 10% in healthy Dutch women), and 5 induced abortions (6%). An impressive 44% of the 70 pregnancies >20 weeks had a complicated course. Four pregnancies (6%) resulted in fetal death, where only 0,9% of these pregnancies result in fetal death in healthy Dutch women. Other complications were pregnancy induced hypertension (6%), pre-eclampsia/HELLP (10%), premature birth (7%) and placental abruption (5%). The frequency of pregnancy complications is (much) higher in cSLE than in SLE or the Dutch female population.
Conclusions. A substantial percentage of females with cSLE sees their disease as a restrictive factor in the wish to have children. Time to pregnancy was not delayed but the frequency of pregnancy complications including fetal death was remarkably high in cSLE patients.

Key words: adult outcomes of cSLE, pregnancy outcomes, patient reported outcomes

S16:05

THE ITALIAN SLE SURVEY BY WEB: INVESTIGATING PATIENTS' UNMET NEEDS AND IMPROVING CARE SYSTEM THROUGH VIABLE ONLINE SURVEY TOOLS

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Objective. In 2015 an online SLE Survey, directed to Italian patients, was carried out by Lupus Italy to investigate perception of chronic illness and the most serious difficulties in everyday life, due to disease itself and to medications. The Survey was also designed to assess chronic pain impact and how patients deal with it. Difficulties related to quality and conditions of health-care provision in Italy were investigated as well.
Design and Method. Questionnaire core items (age, gender, geographic data, disease duration, age at diagnosis, comorbidity, disability degree, care practices, etc.) were set for sample features mapping. Specific items explored subjective incidence and characteristics of pain, e.g. primary or secondary to SLE, and its treatment, if any. The online version was created through Qualtrics platform. SLE patients throughout Italy were informed by social media and other channels (mailing list, website, Facebook); running period of the questionnaire on Gruppo LES Italiano website was April 2015. Participation was voluntary and anonymous. Due to data collection method, the Survey represented mainly patients having access to Internet.
Results. About 550 SLE patients provided comprehensive answers, 94.7% women, 5.3% men; mean age 33 y. (14-82 y. range); 84% received first SLE diagnosis mean age 29 y.(18-42 y. range); very early diagnosis (3-4 y.) up to extremely late diagnosis (>60 y.) were reported; 36% stated comorbidity with 1 up to 6 other autoimmune diseases, mainly APS. Majority declared relevant SLE impact on life, underlining specific problems and needs at different disease stages. Stress is important and worsens illness conditions. Family relational problems are frequent. Perceived need for psychological support covers 54%, but only 25% receives specific advice from physicians. Osteo-articular pain is the main symptom reported (83%). Only 54% use drugs for pain control; physicians seem not to be fully responding to patients' request to take into account the impact of pain. Women workers face many difficulties due to combined factors, which severely reduce access to proper care: lack of dedicated care units and nursing facilities, exclusion from exemption tables for several drug categories, economic barriers and work constraints.
Conclusions. Current healthcare models do not meet patients' complex needs, thus strongly affecting quality of life and doctor-patient relationship. The Survey highlights the importance of physicians' clinical competence and ability to manage patient's crisis moments, in order to deal together with the course of a chronic illness. From 2016 Gruppo LES Italiano will periodically submit an online SLE Survey to the Italian patients, with the aim of better deepening the critical areas arisen in 2015 and providing to disclose the results to all the Institutions involved in social-health policies decision-making.

Key words: LES Web Survey, chronic illness, unmet needs

S16:06

PURE RED CELL APLASIA IN PATIENTS FROM SLE REGISTRY FROM THE SPANISH SOCIETY OF RHEUMATOLOGY (RELESSER)

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Objective. Systemic Lupus Erythematosus (SLE) is an autoimmune systemic rheumatic disease that, in our area, presents hematologic manifestations in approximately 70% of cases[1]. Some of them are very rare; there are no large series whose analysis could provide relevant information.
The objective of our study is to study the characteristics of patients with Pure Red Cell Aplasia (PRCA) in a large sample of SLE patients.
Design and Method. SLE patients from RELESSER database were studied. We analysed the clinical and analytical SLE manifestations at 12 different domains (mucocutaneous, renal, musculoskeletal, constitutional, haematologic, vascular, cardiac, respiratory, neuropsychiatric, gastrointestinal, ophthalmic and serological) before, during and after PRCA diagnosis and until the last available assessment. We also studied activity (SELENA-SLEDAI) and damage (SLICC/ACR DI) indices at each of those times.
We evaluated the treatment received, PRCA recurrences and the number of deaths by this entity.
Results. 3,656 patients from 45 Rheumatology Units across Spain were studied. 5 cases of PRCA were found (<0.5%of total). There were no viral infections in relation with the PRCA.
All patients had a good response to treatment, reaching complete remission without relapses or deaths. The mean number of treatment lines (± SD) that were necessary was 2.2(± 1.01) and the mean (± SD) number of treatments used was 2.8(± 1.92). Except for the patient diagnosed with PRCA before SLE, all of them received glucocorticoids as initial treatment. Of these 4 patients only 1 achieved complete remission without requiring immunosuppressive therapy.
The following table shows the characteristics of each patient:

	Patient1	Patient2	Patient3	Patient4	Patient5	
Number of organ systems affected by SLE before PRCA diagnosis	Not applicable	6	6	4	7	
Number of organ systems affected by SLE at PRCA diagnosis	Not applicable	1	1	1	6	
Number of organ systems affected by SLE until last assessment	3	3	5	1	2	
Haemoglobin levels at PRCA diagnosis (g/dl)	7	4.9	4.9	4.5	6.3	
Bone Marrow biopsy or aspirate	Selective aplasia / hypoplasia of the red series, without changes in other series					
SLEDAI//SLICC-ACR DI at PRCA diagnosis	Not applicable	4 // 1	2 // 1	0 // 0	20 // 0	
SLEDAI//SLICC-ACR DI 1 year after PRCA	Not applicable	0 // 1	2 // 1	2 // 0	4 // 0	
SLEDAI//SLICC ACR DI at last assessment	0 // 0	6 // 3	0 // 2	0 // 0	0 // 0	
Number of treatment lines	2	2	2	1	4	
Treatments administered	1st: Oxitosona	1st: Glucocorticoids	1st: Glucocorticoids	Glucocorticoids	1st: Glucocorticoids e Hidroxicloroquina	2nd: Belimumab y erythropoietin
	2nd: Inmunoglobulins	2nd: Inmunoglobulins & RBC transfusion	2nd: Ciclosporin A		3rd: Rituximab	4th: Darbepoetin alfa
Total number of treatments administered	2	3	2	1	6	
Relapses	0	0	0	0	0	
Deaths	0	0	0	0	0	

Conclusions. PRCA is a very rare cause of anemia in SLE. In most cases it appears several years after the diagnosis of SLE. It is a serious manifestation but in our series, with a proper management showed a favourable response.

Reference
PEGO-REIGOSA JM *et al*.: Analysis of disease activity and response to treatment in a large Spanish cohort of patients with systemic lupus erythematosus. Lupus 2015; 24: 720-9.

Key words: pure red cell aplasia, anemia, hematological manifestations

S17: Neuropsychiatric lupus and antithrombotic therapy

S17:03

ELEVATED INTERFERON-ALPHA CAUSES CEREBRAL MICROVASCULAR DISEASE: A MODEL FOR NEUROLUPUS?

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Objective. Elevated interferon signatures are strongly associated with SLE, yet the downstream effects of interferon on the brain are poorly understood. Given that cerebral small vessel disease is an almost universal feature of neurolupus, we examined the effect of interferon on the cerebral microvasculature, using a focal brain-restricted model of interferon overexpression.
Design and Method. We studied the cerebral microvasculature of transgenic mice which produce interferon-alpha under the control of an astrocyte-specific promoter (GFAP-IFNalpha). The microvasculature of (i) wildtype mice, (ii) transgenic mice with low levels of astrocyte-derived IFN production (GFAP-IFNLow) and (iii) high levels of IFN production (GFAP-IFNHigh) was examined and quantified. Scanning electron microscopy of microvascular casts of wildtype (n=2) and GFAP-IFNHigh mice (n=6) was performed, in addition to quantitative immunohistochemistry. The total number of microvascular abnormalities was counted across three X20 magnification fields per anatomical region (cerebellum, cortex, brainstem, thalamus, hippocampus), with counting performed blind to genotype. Rescue experiments were performed by crossing GFAP-IFNHigh mice to IFNAR-/- mice, which lack a functional type 1 interferon receptor.
Results. We observed a spectrum of small vessel disease associated with interferon overexpression, including microaneursym formation, T-cell infiltration and endothelial hyperplasia. This interferon-associated microangiopathy was dose-dependent (p<0.001 one-way ANOVA). 3D-scanning electron microscopy confirmed the morphological abnormalities and identified microaneursyms arising from capillaries, together with other variations in microvessel calibre. Both upregulation of interferon response genes (IRG) and microvascular disease are fully rescued in IFNHigh x IFNAR1-/- mice with high interferon production, but no functional type 1 interferon receptor.
Conclusions. Transgenic overexpression of interferon-alpha in the brain causes a spectrum of microangiopathy, mediated through IFNAR. Interferon-driven microvascular disease overlaps with the spectrum of cerebral microangiopathy observed in the brains of patients with lupus. Given that interferon represents a modifiable and frequently dysregulated pathway in lupus, further studies are required to determine the degree to which interferon dysregulation might drive the cerebral microangiopathy associated with lupus.

Key words: interferon, microvascular, neurolupus

S17:04

NEUROPSYCHIATRIC MANIFESTATIONS IN PEDIATRIC-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS: EXPERIENCE OF A SPANISH TERTIARY CENTER

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Objective. To analyze the clinical and immunological features of patients with pediatric-onset systemic lupus erythematosus (pSLE) and neuropsychiatric (NP) manifestations followed in a Spanish tertiary center.
Design and Method. We performed a retrospective study of 49 patients with pSLE diagnosed between 1985 and 2005 in our center. The ACR NPSLE case definitions were used for classification. Demographic, clinical and immunological data were obtained through review of their medical charts.
Results. Twenty-six patients (53%) developed NP manifestations. Mean age was 13.6 years and female:male ratio was 2.7:1. NP manifestations were present at the beginning of the disease in 7 cases (26.9%) and the mean time to develop them was 30.5 months. The most common presentations of NPSLE were seizures (50%), headache (26.9%), mood disorder/depression (26.9%), psychosis (19.2%), cerebrovascular disease (15.3%) and aseptic meningitis (15.3%). There was more than one NP manifestation in 15 cases (57.7%), with an average of 2.4 manifestations/patient. The comparison of patients with and without NPSLE demonstrated significant diffences (p<0.05) in the number of males, titers of antinuclear antibodies (ANA) and anti-DNA antibodies, positivity for anti-β2-glicoprotein I (β2GPI) and cryoglobulins, high erythrosedimentation rate (ESR) and low complement (C3, C4) (Table I). There were 2 cases of mortality in NP-

SLE (7.7%) during follow-up period, one as a result of infection of the central nervous system and another due to sepsis associated with intestinal thrombosis.

Table I. Comparison of clinical and immunological features in patients with and without NPSLE.

	Total	NPSLE	Non-NPSLE	*p*-value
Number of patients	49 (100%)	26 (53%)	23 (47%)	-
Females:males	42:7	19:7	23:0	0.0072*
Age at diagnosis (years)	13.2±3.1 (2-18)	13.6±3.3 (2.18)	12.9±2.9 (7-17)	0.4179
Disease duration (months)	19.6±10.8	18.9±11.8	20.2±9.6	0.5387
Secondary antiphospholipid syndrome	8 (16.3%)	5 (19%)	2 (8.6%)	0.0557
ANA ≥ 1/1280	10/40 (25%)	8/21 (38.1%)	2/19 (48.6%)	0.0443*
Anti-DNA antibodies (IU/mL)	117.1	186.2	49.9	0.0042*
Anti-Ro/SSA antibodies	14/46	10/23	4/23	0.0545
Antiphospholipid antibodies	11/40	6(20	5/20	0.7233
Anti-cardiolipin antibodies	4/40	3/20	1/20	0.2918
Antiβ_2GPI antibodies	5/40	5/20	0/20	0.0168*
Lupus anticoagulant	11/39	6/20	5/19	0.7982
Cryoglobulins	6/18	6/12	0/6	0.0339
ESR (mm/h)	23.2	25.1	13.5	0.0108*
C reactive protein (mg/L)	3.5	5	2.6	0.2077
C3 (mg/dL)	66.1	54.4	75.7	0.0042*
Low C3 (<80 mg/dL)	32/46	20/23	12/23	0.0104*
C4 (mg/dL)	11.7	7.2	15.4	0.0037*
Low C4 (<16 mg/dL)	14/46	20/23	11/23	0.0046*

Conclusions. In our series >50% of patients had NPSLE manifestations and frequently occured early during the course of the disease. The clinical spectrum of NPSLE was wide in our cases and most of them had more than one manifestation. Patients with NPSLE showed a higher disease activity as measured by levels of autoantibodies, increased acute-phase reactants and low complement. Although NPSLE has been associated with antiphospholipid antibodies in other series, specifically anticardiolipin antibodies and lupus anticoagulant, we only found significant association with anti-β2GPI antibodies. Mortality in patients with NPSLE was high.

Key words: neuropsychiatric lupus, pediatric-onset SLE

S17:05

EVIDENCE OF ALTERED BLOOD BRAIN BARRIER PERMEABILITY IN SYSTEMIC LUPUS ERYTHEMATOSUS USING MAGNETIC RESONANCE IMAGING

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Background. Neurocognitive dysfunction is a common manifestation of childhood-onset Systemic Lupus Erythematosus (cSLE). Murine models suggest that loss of the blood-brain barrier (BBB) integrity allows brain-reactive proteins to enter the CNS and contribute to SLE-associated pathology. Contrast magnetic resonance imaging (MRI) can provide a measure of BBB integrity, but has risk associated with gadolinium use. We have previously identified multiple areas of gray matter (GM) loss on structural MRI in cSLE patients with neurocognitive deficits. Our aim was to evaluate safe, non-invasive MRI-methods of measuring regional BBB permeability and its relationship with neurocognitive function and regional GM volume in cSLE.
Methods. Twelve cSLE patients and 12 healthy controls (age, gender, race and socioeconomic status matched) were enrolled. Those with diseases or medications (except prednisone) affecting neurocognitive function were excluded. Cognitive performance was assessed using the cSLE Neurocognitive Battery, which probes four cognitive domains: working memory, psychomotor speed, attention, and visuoconstructional ability. Performance in each of these was standardized and expressed as a Z-score. We almost concurrently performed arterial spin labeling (ASL) and diffusion-weighted imaging to measure regional BBB permeability. Voxel-based morphometric analysis was done to measure regional GM volume. Voxel-wise comparisons of capillary permeability were made between the cSLE and control groups. Correlation analysis was performed between regional BBB permeability and cognitive performance Z-scores, as well as local GM volume for the cSLE group.
Results. Among the cSLE patients (11 females, 7 African American, mean age 18 ± 6.8 years), 9 were treated with prednisone (median dose 5 mg/d). None was diagnosed with active neuropsychiatric SLE. Group comparison revealed clusters of voxels with significantly greater BBB permeability for cSLE patients than controls, in three regions as shown in Figure 1. Correlations between BBB permeability and regional GM volume or overall and individual domain Z-scores for neurocognitive performance were not statistically significant, although locations of significant increases in permeability for cSLE closely match our previously identified areas of GM loss and functional changes associated with clinically overt neurocognitive impairment.

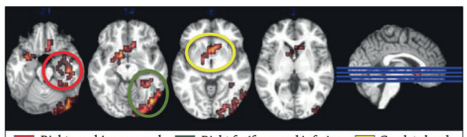

Figure 1: Select slices of a group difference T map for Blood-Brain Barrier permeability (SLE>controls). The three identified significant clusters (< 0.05 family-wise error corrected) are shown with legend.
[Red indicates decreased Blood-Brain Barrier integrity]

Conclusions. We present imaging evidence of altered regional BBB permeability in cSLE, using a novel non-invasive MRI technique. The absence of correlation with GM volume or cognitive performance Z-scores, yet similar location to GM loss in previous work in our cSLE cohort suggests that BBB breakdown may precede clinically overt neurocognitive impairment and brain tissue loss. Longitudinal studies are needed to confirm the change in GM volume in relation to BBB permeability over time.

Key words: blood-brain barrier, MRI, NPSLE

S17:06

ANTICOAGULATION AND LONGTERM OUTCOMES IN PATIENTS WITH RENAL ARTERY STENOSIS AND ANTIPHOSPHOLIPID SYNDROME

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Background. Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome (APS) (26%) compared to the general hypertensive population (8%), and anticoagulation with INR>=3 was associated with initial reduction of chronic kidney disease (CKD) and hypertension.
Objectives. To assess the long-term outcome in patients with APS with RAS. To assess the efficacy of anticoagulant therapy and the prevalence of chronic kidney disease and death in patients with renal artery stenosis and APS.

Patient Group	CKD	ESRD	Death
Anticoagulation (23)	15/23	4/23	5/23
No anticoagulation (14)	6/14	2/14	4/14
p value	0.3	1.0	0.7
APS (15)	7/15	3/15	1/15
APS+autoimmune disease (22)	14/22	3(22	5/22
p	0.3	0.7	0.4
Medical therapy (28)	13/28	3/28	7/28
Angioplasty (9)	8/9	3/9	2/9
p	0.05	0.14	1

Design and Method. In our departmental database we identified 37 patients with RAS and APS fulfilling Sapporo criteria: anticardiolipin IgG/IgM titer>40 units or >99thpercentile (or +lupus anticoagulant) on >=2 occasions >=6 weeks apart AND vascular thrombosis (or pregnancy morbidity). RAS was diagnosed by magnetic resonance angiography (MRA).
Results. 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had previous thrombosis. 7/37(18.9%) had bilateral RAS, 3 artery occlusion. 6/37(16.2%) had concurrent coeliac stenosis. Recanalization of RAS occurred after hydroxychloroquine in 3/37 and 9/37(24.3%) underwent angioplasty ± stenting. MRA was repeated in 11/37(29.7%) after 2 years. 23/37(62.2%) were anticoagulated, with 9/37(24.3%) on antiplatelet therapy. 13/37(35.1%) received hydroxychloroquine, 10/22(45.5%) immunosuppressives and 18/37(48.6%) antihypertensives. 9/37(24.3%) died after a median of 10 years since RAS diagnosis. 21/37(56.8%) developed CKD: 6 endstage renal failure (ESRD) and 15 with median eGFR 39 mls/min.
Conclusions. The majority of patients with RAS and APS were female, developed CKD and did not benefit from angioplasty. Anticoagulation was not associated with long-term reduction of ESRD or death, suggesting a non-thrombotic pathogenic process underlying RAS, e.g. intimal hyperplasia. Treatment of associated vascular risk factors and underlying autoimmune disease is paramount. Anticardiolipin antibodies and renal MRA are useful for screening hypertensive lupus patients.

Key words: antiphospholipid, renal, artery

S18: SLE activity, damage and prevention

S18:03

IMMUNE COMPLEXES CONTAINING SERUM B-CELL ACTIVATING FACTOR AND IMMUNOGLOBULIN G CORRELATE WITH DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. 'B-cell activating factor belonging to the TNF family' (BAFF or BLyS) is important for the survival of autoreactive B-cells in systemic lupus erythematosus (SLE). However, the association between serum BAFF levels and SLE disease activity is controversial. Independently, autoantibodies targeting BAFF (IgG anti-BAFF) have also been described in SLE patients and were found to be associated with disease activity. The aim of our study was to analyze the relationship between SLE disease manifestations and serum levels of BAFF, IgG anti-BAFF and BAFF-IgG complexes.
Design and Method. Levels of serum BAFF, IgG anti-BAFF and BAFF-IgG complexes were quantified by ELISA. IgG anti-BAFF and BAFF-IgG complexes were further characterized using serum fractions obtained by fast protein liquid chromatography. To study the association of serum BAFF, IgG anti-BAFF and BAFF-IgG complex levels with SLE manifestations, 373 visits from 178 patients prospectively included to the Swiss SLE Cohort Study were analyzed.
Results. While IgG anti-BAFF levels were not associated with clinical manifestations of SLE, serum BAFF levels correlated with disease activity and renal involvement. Interestingly, we could also demonstrate the occurrence of small as well as large BAFF-IgG complexes in the sera of SLE patients that were not due to a treatment with belimumab and differed from *in vitro* constructed complexes. Most strikingly, the levels of these BAFF-IgG complexes were found to strongly correlated with overall disease activity, low complement levels and a history of lupus nephritis.
Conclusions. BAFF-IgG complexes strongly correlate with disease activity in SLE patients suggesting a pathogenic role in systemic lupus.

Key words: serum BAFF, Ig anti-BAFF autoantibodies, BAFF-IgG complexes

S18:04

AUTOIMMUNE HEMOLYTIC ANEMIA AND THROMBOCYTOPENIA IN A SINGLE CENTRE COHORT OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS FROM TURKEY: CLINICAL ASSOCIATIONS AND EFFECT ON DISEASE DAMAGE AND SURVIVAL

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Objective. Hematologic involvement is common in patients with SLE. Thrombocytopenia and AIHA, prevalences of which have been reported as 10-40 % and 5-10 % respectively, have considerable impact on prognosis. Herein, we aimed to investigate the frequencies of these hemocytopenias, their clinical and serological associations and effect on disease outcome in a large single centre cohort of patients.
Design and Method. We analysed our cohort of 852 patients who fulfilled at least 4 of the ACR criteria for SLE. The data presented was the cumulative clinical and serological manifestations throughout the follow-up period. Hemolytic anemia was defined as a drop in hemoglobin accompanied by increased reticulocyte count, high serum lactate dehydrogenase and reduced haptoglobin levels in the presence of a positive Coombs' test. Thrombocytopenia was defined as a platelet count of <100x109/mm^3. Demographic characteristics, clinical features, autoantibody profiles, damage and mortality data retrieved from the database were compared between patients with and without each hematological abnormality. The $\chi 2$ test, logistic regression and Kaplan-Meier survival analyses were used.
Results. There were 93 (10.9%) patients with AIHA and 215 (25.3%) with thrombocytopenia. Patients with AIHA were significantly younger at diagnosis (27±13 vs 31±12, p<0.05) and had a significantly shorter disease duration (95±84 vs 118±85 mo, p<0.05). AIHA and thrombocytopenia were both associated with neuropsychiatric (NP) involvement (p<0.05) and associated with each other (p<0.05) and leukopenia (p<0.05). Comparison of patients with AIHA or thrombocytopenia to the rest of the cohort displayed significant associations with antiphospholipid syndrome (APS), anticardiolipin (aCL) antibodies and lupus anticoagulant (LA). In patients with thrombocytopenia the relationship with APS features, namely thrombosis and pregnancy morbidity, was stronger (p<0.001).
Compared to the rest of the cohort, more patients in both groups had organ damage and their mean SLICC damage score was significantly higher. Association to NP damage was discernible in both groups (p<0.05). In addition, damage in renal and cardiovascular domains and diabetes were more pronounced in patients with thrombocytopenia (p<0.001)
Kaplan Meier survival analysis showed that patients with AIHA had significantly reduced survival rates at 10 (94 vs 77%) and 20 (88 vs 77%) years (p<0.001). In the thrombocytopenia group, despite the lack of significant differences, there was a tendency for lower survival rates.
Conclusions. We demonstrated that both AIHA and thrombocytopenia were associated with aCL antibodies, coexisting APS and NP involvement and damage in our cohort. There was a strong link between AIHA and thrombocytopenia. Patients with AIHA had a younger age at disease onset with reduced survival. No significant reduction in survival rates was observed in patients with thrombocytopenia. However, besides NP involvement, thrombocytopenia delineated a subgroup of patients with a higher renal and cardiovascular damage which perceivably can affect prognosis. Overall, AIHA and thrombocytopenia may predict a poorer outcome in patients with SLE.

Key words: autoimmune hemolytic anemia, thrombocytopenia, systemic lupus erythematosus

S18:05

CHRONIC DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS: EVOLUTION AFTER 5-YEAR FOLLOW-UP

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Objective. The prevention of chronic damage represents one of the most important target in the management of SLE patients. About 50% of patients develop chronic damage, especially in the early disease phase, related to disease activity, treatment adverse events and comorbidities. Longitudinal studies demonstrated a progressive increase of damage, evaluated by using SLICC Damage Index (SDI). Moving from these evidences, we aimed at evaluating the progression of chronic damage in a monocentric SLE cohort after 5 years.
Design and Method. We analyzed 413 SLE patients diagnosed according to the American College of Rheumatology 1997 revised criteria, referring to a dedicated out-patient clinic. Clinical and laboratory data were collected in a standardized, computerized and electronically-filled form, including demographics, past medical history, comorbidities and concomitant treatments. In all patients, chronic damage was determined by using SDI, with the evaluation of 12 organ systems.
Results. According with the study protocol, we evaluated only patients with a minimum follow-up of 5-years. Eighty-eight patients were followed for at least 5 years in the out-patient clinic (8M/80F, mean age 47.8±12.3, mean disease duration 17.4±8.1 years). At the first visit, 50 patients (56.8%) did not show damage, while the remaining 38 showed SDI>0, with a mean ±SD value of 1.8±1.4. Patients with damage showed a significantly higher mean age and disease duration (p<0.0001, p=0.0013 respectively).
We revaluated these patients after 5 years. The progression of damage was registered in 25 patients (28.4%) with a significant increase of SDI values (baseline: median 0.0 95% CI 1.85-3.0; follow-up: median 1.0 95% CI 3.0-6.8; p=0.03).
We observed the appearance of damage in 12/50 (24%) patients with SDI=0 at baseline: the muscuolo-skeletal system was the most frequently involved, with damage in 5/12 patients (41.6%). When evaluating patients with SDI>0 at baseline, we identified a progression of damage in 13 subjects (34.2%). In this subgroup, neoplasms were the most frequently developed during the follow-up (4/38, 10.5%).
The comparison of frequency of autoantibodies identified a significantly higher prevalence of anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, antiphospholipid antibodies in patients with progression of chronic damage (p=0.0007, p=0.02, p=0.02, p=0.01, p=0.00006, respectively).

Conclusions. In our study, we demonstrated a progression of chronic damage in almost 30% of SLE patients after 5 years. In particular, the progression was more frequent in patients with SDI>0 at the baseline. Moreover, the increase of SDI was associated with the positivity for several autoantibodies. Our results underline the need of a better management of SLE patients in order to prevent damage accrual.

Key words: chronic damage, progression, autoantibodies

S18:06

SLICC DAMAGE INDEX IS A PREDICTOR FOR HOSPITALIZATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS: A 7-YEAR COHORT STUDY OF 297 PATIENTS FROM A TERTIARY REFERRAL CENTRE

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Objective. To determine risk factors for hospitalization in patients with systemic lupus erythematosus (SLE).
Design and Method. We included patients fulfilling the ACR-revised and/or the SLICC classification criteria for SLE and regularly followed at a University hospital-based Lupus clinic. Patient data was prospectively collected in the SLE Clinic cohort database, complemented with review of hospital discharge reports. Data from January 1, 2009 up to December 31, 2015 were included. Outcomes for this study were time from baseline to first event of hospitalization, categorized into: i) hospital admission due to SLE disease activity; ii) hospitalization due to any other causes, excluding SLE disease activity. For each of these outcomes, we analyzed as potential clinical predictors at baseline: gender; age at disease onset; age at study baseline; SLE classification criteria (ACR vs SLICC alone); lupus nephritis; SLICC-Damage Index (SDI), categorized as SDI=0 (no damage) or SDI>0 (any damage); SLEDAI-2k score; antimalarial use; immunosuppressive therapy and prednisone daily dose. We carried a two-step statistical analysis for each hospitalization outcome: first, survival analysis with Kaplan-Meyer curves and log-rank tests for each potential predictor; secondly, we applied multivariate Cox models to estimate hazard ratios (HR) for significant predictors. *p*-values <0.05 were considered statistically significant.
Results. We included 297 patients (87.2% female, mean age: 42.5±14.4 years, mean disease duration: 11.3±9.1). During a median follow-up of 85.2 months (IQR: 60.8-85.1), 47% of the patients were hospitalized at least once (25.6% with admissions due to active SLE and 37.0% hospitalized due to other causes). In the univariate analysis, SLEDAI-2k score >5 ($p<0.0001$), immunosuppressant use ($p<0.0001$), prednisone dose >10mg/day ($p<0.05$), and SDI >0 ($p<0.001$) were significantly associated with higher risk, and antimalarial use ($p<0.05$) with lower risk of hospitalization due to active SLE; the only predictor of hospitalizations for other causes was SDI >0 ($p<0.01$).
In the multivariate Cox models, any irreversible damage at baseline (SDI>0) was predictive both for hospitalizations due to SLE disease activity (HR 2.18, 95%CI 1.26-3.76, $p<0.01$) or due to any other causes (HR 1.82, 95%CI 1.17-2.83, $p<0.01$). Immunosuppressant use (HR 2.18, 95%CI 1.26-3.76, $p<0.01$) and SLEDAI-2k score (HR 1.10, 95%CI 1.02-1.20, $p<0.01$) were predictive only for hospitalizations due to active SLE.
Conclusions. The need for hospitalization is higher in SLE patients with established organ damage, as well as in those with more active SLE or severe disease requiring immunosuppressants.

Key words: hospitalization, SLICC-Damage Index, SLEDAI-2k

S19: SLE registries and cohorts (2)

S19:04

CHRONOLOGICAL ANALYSIS OF DAMAGE ACCRUAL IN SLE PATIENTS FROM THE SPANISH REGISTRY (RELESSER)

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Objective. To study damage manifestations and the temporal relationship of their appearance with the time of SLE diagnosis.
Design and Method. In the first RELESSER phase, accumulated information on 400 variables per patient at the last evaluation was collected.
Cumulative incidence function for damage was estimated. The impact on mortality was studied controlling for sex, race, age at diagnosis and delay of SLE diagnosis by Cox regression.
Results. 2,662 patients had the dates of damage events: 2,417 (91.0%) women, 2,402 (92.8%) Caucasian, mean age (±SD) 34.0(±13.6) years at the time of diagnosis. The mean follow-up time was 115.6(±50.8) months. 112 (4.2%) died. At the study time 917 (34.4%) had at least 1 damage manifestation, the mean number of systems per patient with at least 1 damage manifestation was 0.54(±0.92). The mean SDI score was 0.65(±1.2). The systems more frequently damaged were musculoskeletal (11.9%), ophtalmic (7.8%) and cardiovascular (5.9%). Damage cumulative incidence (CI95%) in at least 1 system in the first year, five years and after more than ten years was 7.4% (6.4-8.4), 18.9% (17.3-20.4) and 29.2% (27.3-31.1) respectively. The systems damaged earlier, 1 year after SLE diagnosis, were: musculoskeletal 1.7% (1.2-2.2), neuropsychiatric 1.3% (0.8-1.7), renal 1.2% (0.8-1.6) and cardiovascular 0.9% (0.6-1.3). The increase rate of damage is significantly higher short time after SLE diagnosis. The proportion of patients with damage in at least 1 system at 5 and 10 years was 18.9% (17.3-20.4) and 29.2% (27.3-31.1). While in the first year 7.4% of patients present damage in any system, only 2.9% per year do so since the first to the fifth year after diagnosis. Between the fifth and tenth year there was only an annual increase of damage of 2.1%. Risk of death is multiplied by 2.04 (1.7-2.3) when a new system is damaged. Significant impact on neuropsychiatric, renal, pulmonary, cardiovascular systems and malignancy was found, with multiplicative risk factors of 2.0, 1.8, 2.8, 1.7 and 2.7 respectively.
Conclusions. Damage occurs in early stages of the disease, appearing early in musculoskeletal, neuropsychiatric and kidneys. The increase of damage is greater in the first year after SLE diagnosis. Accumulation of visceral damage increases the mortality rate.

Key words: chronological, damage, cohort

S19:05

ANTI-PHOSPHOLIPID ANTIBODY PREVALENCE AND CARDIOVASCULAR MORBIDITY IN THE GENERAL POPULATION OF THE CAMELIA STUDY

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Objective. An accurate estimate of the prevalence of serum anti-phospholipid antibodies (aPLs) in the general population remains to be determined, as well as the influence of aPLs on cardiovascular (CV) risk and events.
Design and Method. The CAMELIA cross-sectional study included 1,712 adult subjects randomly enrolled in 2010 from the voting list of a representative city in the Milan region (50.2% men, median age 47 years, interquartile range 37-61, 18% obese, 26% smokers, 22% with hypertension, 53% with dyslipidemia, 6% with diabetes). Serum IgG, IgM, and IgA anti-cardiolipin (aCL), anti-beta 2 glycoprotein I (aGPI), and anti-phosphatidylserine-prothrombin (aSP) antibod-

ies were tested by commercially available ELISA and considered at high titer (HT) when >40UI. Doppler ultrasound of the carotid artery, with intima-media thinckness (IMT, expressed as mean max) and interadventitia common carotid diameter (ICCAD), which reflects subclinical atherosclerosis, was available in a randomly selected third of the cohort. CV risk factors and acute events (acute myocardial infarction, stroke, and peripheral arteriopathy) were recorded by physician-assisted questionnaires; the Framingham risk score was used to determine the 10-year CV risk. The statistical analyses included univariate comparisons and multivariate models including significant associations.

Table I. Anti-phospholipids antibodies prevalence in the CAMELIA cohort.

Antibody	Total
aPL positive	259 (15.1%)
>1 aPLs	35 (2%)
aPL HT	56 (3.3%)
>1 aPL HT	15 (0.9%)
aCL	26 (1.5%)
aCL HT	17 (1%)
aCL single aPL	2 (0.1%)
aCL IgG	15 (0.9%)
aCL IgG HT	11 (0.6%)
aCL IgM	18 (1.1%)
aCL IgM HT	10 (0.6%)
aCL IgA HT	4 (0.2%)
aGPI	73 (4.3%)
aGPI HT	48 (2.8%)
aGPI single aPL	54 (3.2%)
aGPI IgG	20 (1.2%)
aGPI IgG HT	3 (0.2%)
aGPI IgM	28 (1.6%)
aGPI IgM HT	6 (0.4%)
aGPI IgA	35 (2%)
aGPI IgA HT	12 (0.7%)
aSP	201 (11.7%)
aSP HT	29 (1.7%)
aSP single aPL	167 (9.8%)
aSP IgG	157 (9.2%)
aSP IgG HT	19 (1.1%)
aSP IgM	65 (3.8%)
aSP IgM HT	12 (0.7%)

aCL: Anti-cardiolipin; aGPI: anti beta 2 glycoprotein I; aSP: anti-phosphatidylserine-prothrombin; HT: high titer.

Results. Table I illustrates the serum aPL prevalence. Serum aPL was associated with older age, in particular for aGPI and aSP, while HT aCL IgG and aSP IgG were more frequent among smokers but we found no major differences between sexes. Hypertension and hypercholesterolemia were more prevalent in aGPI IgG and IgM positive subjects, respectively. The Framingham highest risk score (>20%) was more frequently seen with positive aCL. Serum aGPI were significantly associated with increased IMT Mean Max, although dependent on traditional CV risk factors at multivariate analysis, and increased ICCAD average (beta coefficient 0.51, p=0.003 for aGPI IgA after adjustment for CV risk factors). In subjects with high CV risk (Framingham risk score >20% and/or diabetes and/or BMI >35), serum aPL was associated with a higher risk of CV events (odds ratio 2.52, 95% confidence interval 1.24-5.11, p=0.011). In particular, aCL positivity was associated with higher incidence of peripheral artheriopathy and myocardial infarction.
Conclusions. We report that serum aPL are frequently found in a large unselected sample from the general population, equally distributed in men and women, and are associated with many known CV risk factors, moreover, aPLs are apparently an additional risk factors for CV events in high risk population.

Key words: epidemiology, cardiovascular disease, gender medicine

S19:06

CAUSES OF MORTALITY AMONG FILIPINO PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN A SINGLE TERTIARY HOSPITAL

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Objective. To describe the causes of mortality among Filipino patients with systemic lupus erythematosus (SLE) in a single tertiary hospital.
Design and Method. This study describes the primary and secondary causes of death among Filipino patients with SLE included in the University of Santo Tomas (UST) Hospital Lupus Database from 2005 to 2015. Records of death were obtained from clinics, hospital records, and first hand information from family members. The causes were categorized as SLE- or non-SLE related, and analyses included standardized mortality rates (SMR) and any variations between pediatric vs. adult-onset SLE. Unknown causes of death were excluded from further analysis.
Results. The UST Lupus Database 2005-2015 included 2,474 patients with a mean disease duration of 6.46 + 5.64 SD years; SMR was calculated as 3.68. Among a total 269 patients (248 females, 92%) with known causes of death, 38 (14%) had pediatric onset and 231 (86%) had adult onset SLE. Deaths related to active SLE 146(54%) were the most common both in pediatric and adult onset SLE, followed by infection 67(25%), with concomittant active SLE and infection as contributors to mortality in 37(14%) of patients. Among the SLE related causes of death, renal involvement accounted for 10(50%) among pediatric onset and 49(39%) among adult onset as the main cause of death while infection due to sepsis in pediatric onset 7(88%) and adult onset 40(68%) was the main cause of non-SLE related deaths with more sepsis among pediatric onset SLE.
Conclusions. In this cohort of Filipino patients with SLE, active disease particularly renal involvement, as well as infection were the main contributors to mortality. This strongly underscores both the dilemma and need for more aggressive disease control while concomitantly finding ways to avert the immunosuppressive side effects of therapy.

Key words: systemic lupus erythematosus, Filipino, mortality

S20: APS and SLE

S20:04

PHOSPHATIDYLSERINE/PROTHROMBIN ANTIBODIES IN PREGNANT PATIENTS WITH SLE AND ANTIPHOSPHOLIPID SYNDROME

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Objective. Despite the substantial improvement in the last years, the pregnancy outcome in patients with antiphospholipid syndrome associated to Systemic Lupus Erythematosus (SLE) remains unsatisfactory. Assessment of antibodies recognizing the phosphatidylserine/prothrombin complex (aPS/PT) might be useful in establishing the risk of thrombosis in patients with SLE. Relatively little is known about the potential association of these antibodies to pregnancy complications.
Design and Method. This ongoing study has so far included 48 patients from two referral centers in Italy, the Ospedale San Raffaele in Milano and the University Hospital of Padua. We have assessed the presence of aPS/PT antibodies in consecutive pregnant patients with SLE and antiphospholipid syndrome (SLE-APS, n=12) and in patients with primary APS (pAPS, n=36). We recorded demographic and anamnestic data at the first visit (6–8th gestational week) and prospectively collected data during pregnancy. aPS/PT were assessed using QUANTA Lite ELISA tests (INOVA Diagnostic Inc) on blood samples collected during and out of pregnancy. LLAC, anti-β2-glycoprotein-I, and anti-cardiolipin Abs were in parallel assessed.
Results. The prevalence of aPS/PT was 63.8 % in patients with pAPS (23 /36) and 75% in patients with SLE-APS (9/12). A significant association between the presence of aPS/PT and late pregnancy complications, which include intrauterine death, preeclampsia, IUGR, and preterm delivery, was detected in patients with pAPS (18/21 aPS/PT+ versus 7/15 aPS/PT-; *p* value= 0.025; chi-squared= 6.287; OR= 6.857; IC=1.4 - 33,5) but not in patients with SLE-APS, possibly because of the limited sample size. The presence of aPS/PT was significantly associated with the presence of LLAC (*p* value= 0.001) and of anti-β2-glycoprotein-I abs (*p* value= 0.002) but not of anticardiolipin antibodies.
Conclusions. aPS/PT could represent a promising biomarker in pregnant patients with SLE and pAPS. Larger groups of patients need to be studied they might be of clinical utility in stratifying the patient population based on the risk of pregnancy complications.

Key words: pregnancy, IUGR, PS/PT

S20:05

ANTIPHOSPHOLIPID ANTIBODIES AND LOW COMPLEMENT LEVELS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: ASSOCIATION WITH CLINICAL MANIFESTATIONS AND PROGNOSIS

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Objective. To establish the prognostic impact of Antiphospholipid Antibodies (APL) and low complement levels in the different clinical manifestations of Systemic Lupus Erythematosus (SLE).
Design and Method. 322 consecutive SLE patients (age 41.7±11.6 years, 80% female, disease duration 15.3±6.5 years) have been considered, 289 (90%) with joint involvement, 273 (85%) with cutaneous involvement, 201 (63%) with hematologic involvement, 82 (26%) with serositis, 123 (39%) with lupus nephritis (LN) and 106 (33%) with neuropsychiatric Systemic Lupus Erythematosus (NPSLE). The follow-up data were obtained, and the analysis was conducted to determine the association of APL seropositivity (APL+: lupus anticoagulant, anticardiolipin, anti-beta-glycoprotein1)) with complement consumption and its prognostic value in all clinical subsets.
Results. A significantly higher percentage of patients with at least one APL+ had low complement levels (at least one component) compared to those with APL seronegativity (APL-) (38/97, 39.2% vs 41/223, 18.4%; $p<0.01$) as well as each complement component reduction had a significant correlation with APL+ (36/98, 36.7% patients with low C3/APL+ vs 33/223, 14.8% with low C3/APL-; $p<0.01$; 23/98, 23.5% patients with low C4/APL+ vs 22/221, 10% with low C4/APL-; $p=0.001$). Considering specific organ involvement, there was no association between APL+ and organ involvement except for neurological involvement (63.3% patients with NSPLE and APL+ vs 19.9% APL-; $p<0.01$).
In terms of prognosis there was no significant correlation between APL+ and clinical outcome in joint, hematologic and serositic subsets, whereas a significantly higher percentage of LN patients with APL+ had a worse renal outcome with respect to APL- LN patients (17/40, 43% vs 24/84, 28.6%, respectively; $p=0.005$). Also for cutaneous disease, we observed a worse progression in APL+ patients (5/81, 6.2% APL+ patients vs 7/193, 3.6 % APL-, $p=0.05$), as well as for neurological involvement (32/32, 51.6% APL+ patients vs 7/46, 15.2% APL- patients; $p<0.01$). Hovewer we found no significant correlation between the number of positive APL antibodies with renal and neurologic outcomes. Moreover, low complement levels were not significantly associated with a poor outcome in all clinical subsets, included renal involvement.
Conclusions. Our data show a significant association between complement reduction and APL seropositivity in SLE patients, but APL seropositivity can be considered as a predictive factor of poor renal and neurological outcome, independently from complement reduction.

Key words: antiphospholipid antibodies, complement consumption, clinical outcome

S20:06

RISK FACTORS FOR A THROMBOTIC EVENT IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID ANTIBODIES: A PROSPECTIVE 10-YEARS FOLLOW-UP STUDY

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Objective. To prospectively assess in a 10-years follow-up period risk factors for a thrombotic event in patients with Systemic Lupus Erythematosus (SLE) and confirmed antiphospholipid (aPL) antibody
Design and Method. Inclusion criteria were age >18 years, diagnosis of SLE based on ACR criteria and at least two consecutive positive aPL results. Demographic, laboratory and clinical parameters were collected at enrollment, once a year during the 10-years follow-up period and at the time of the thrombotic event, whenever that occurred.
Results. 55 SLE [6 male, median age at entry 39 yrs (18-85) patients] were prospectively observed between March 2006 and March 2016. A thrombotic event (3 venous, 1 arterial) occurred in 4 subjects (annual incidence rate 0,72%). Multiple aPL positivity, previous thrombotic event and additional risk factors (surgery, INR<2, conventional cardiovascular risk factor e.g. high BMI, hypertension) were more frequently observed in patients who experienced a thrombotic event during the follow-up. The presence of more than one additional risk factor other than aPL was identified by multivariate logistic regression analysis as predictive for thrombosis (HR 3.4, 95% CI 1.2 to 14,7 $p<0.05$).
Conclusions. In a 10-year follow-up, the presence of multiple risk factors in addition to aPL is predictive for thrombosis in SLE patients. Tailored approaches including controlling conventional cardiovascular risk factors and thromboprophylaxis in high-risk situations in these patients is mandatory.

Key words: thrombosis, long term follow up, aPL

S21: Neonatal lupus and other pregnancy-related concerns

S21:04

EFFICACY AND SAFETY OF MODIFIED-RELEASE PREDNISONE IN SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCIES

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Objective. Systemic lupus erythematosus (SLE) is an autoimmune disease that primarily affects women of childbearing age. Despite the overall favorable outcome, pregnancy still represents a challenge. Since the complications are linked to the disease activity, remission is recommended before planning a pregnancy. Prednisone represents a cornerstone in SLE management and is safely used, at low doses (<7.5 mg daily), during pregnancy. Modified-release prednisone (MRP) optimize corticosteroid treatment strategy in both rheumatoid arthritis and polymyalgia rheumatica, thanks to its capability of respect the physiological cortisol circadian secretion. MRP has been approved from FDA in SLE treatment, but no data are available regarding its administration during pregnancy. We aimed to investigate whether this drug is safe and effective as the immediate release prednisone (IRP) in SLE pregnant patients.
Design and Method. We retrospectively evaluated 9 female patients, fulfilling the ACR criteria for SLE, consulting our Centers in a 4-years observation. All of them experienced a successful pregnancy during the observation. Cases were taking low-dose MRP (5 to 7.5 mg/daily) as a baseline treatment, from at least 6 months. They were matched to 9 controls (SLE patients with the same age and duration of disease, taking the same prednisone dose in the IR formulation). Overall pregnancy outcome features; SLE activity (calculated at least once during pregnancy, SLEPDAI) and at baseline/post-partum (SLEDAI) score; patient's global assessment (VAS) at baseline, during pregnancy and in postpartum (mm); need of treatment changes throughout pregnancy and at postpartum (%) were assessed. Homogeneity tests, percentages and scores comparison were run out by non-parametric statistical analysis.
Results. Mean MRP age group was 26±7.2; disease duration, 4±8 years; IR one, respectively, 28±6 and 3± 9 (p=ns). SLEDAI at baseline was 1±0.1 among MPR and 1±0.3 among IR women; SLEPDAI, 1±0.9 and 2±0.2 (p=ns). No major perinatal complications were detected. Preterm births, cesarean section rates, newborns weight and APGAR scores did not differ between the two subpopulations (p=ns). SLEDAI assessed at postpartum was 2.8±0.6 in MRP subjects and 3.4±0.4 in IR (p<0.05). Patients VAS evaluation (MRP vs IR) were, respectively, 3±0.4 and 2±09 at baseline (p=ns); 2±0.6 and 4±0.7 during pregnancy (p<0.05) and 3±0.3 and 4±0.9 at postpartum (p<0.05). Regarding treatment regimen changes, 1/9 (MRP) and 5/9 (IR) women were involved (p<0.05).
Conclusions. Activity (SLEDAI) score was significantly higher in IR patients during postpartum; treatment had to be significantly increased in this subpopulation, in comparison to the MRP one, to manage SLE. VAS evaluation, at the opposite, was significantly different (higher among IR), both during pregnancy and postpartum, again in IR. Minor and expected complications rates did not differ between the two subpopulations. Despite the limited number of subjects, MRP treatment seems to be as safe, but more effective, than standard IR one, during pregnancy of SLE-affected women.

Key words: systemic lupus erythematosus, pregnancy, prednisone

S21:05

1ST TRIMESTER COMBINED SCREENING AND AUTOIMMUNE DISEASES: IMPACT OF PRE-ANALYTICAL VARIABLES ON RISK ASSESSMENT

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Objective. The main goal is to assess the impact of autoimmune diseases (AID) on biochemical parameters PAPP-A and free Beta-hCG individual MoM's, namely high false positive risk rates.
Design and Method. Pregnant women who performed a 1st trimester prenatal screening for aneuploidies at King's College Hospital (UK) between March 2006 and February 2011 (n=48,303 singleton pregnancies), were assessed (11+0-13+6 weeks of gestation) by means of medical history, ultrasound scan (gestational age from CRL; NT; major foetal anomalies screening) and measurement of serum PAPP-A and free Beta-hCG (DELFIA Xpress). Individual risk for trisomy 21/18/13 was estimated, and chorionic villus sampling or amniocentesis for karyotyping was offered to every high-risk case. Karyotype results and pregnancy outcomes were also registered.
Results. From the 48,303 cases, 2,449 were excluded due to missing outcome data. The final population included 45,493 non-autoimmune pregnant women (NAI), plus 361 pregnant women with autoimmune pathology (AI). Median maternal age was significantly different between AI (33.1 y) and NAI (32.1 y) groups, as well as median gestational age at delivery (AI=39.5 w, NAI=40.1 w). All types of AI conditions (APS, CD, RA, UC, MS, others) [1] had significant differences concerning maternal age, except for the MS (n=48, 32.4 y) and the SLE (n=51, 31.8 y) groups. Regarding gestational age at delivery, the differences found in AI population were due to CD (39.2 w), RA (39.8 w) and SLE (38.9 w). There was a significant increase of free Beta-hCG (MoM's) in AI population (1.1) versus NAI population (0.99). The increased free Beta-hCG MoM's in stratified AI groups was derived from MS (1.11), RA (1.13) and SLE (1.40) groups, which had similar gestational age and TN values. False positives rates in AI population (13.57%) were mostly found in the NT<3.5 and positive biochemical group (11,36%). Free Beta-hCG in SLE population presenting false positive risk for Trisomy 21 was 2.124 MoM's.
[1] APS-Anti-Phospholipid Syndrome; CD-Crohn's Disease, RA-Rheumatoid Arthritis, UC-Ulcerative Colitis, MS-Multiple Sclerosis, Others-Miscelaneous.
Conclusions. We found an impact of autoimmune diseases on free Beta-hCG individual MoM's, especially in MS, RA and SLE. The presence of SLE seems to be associated with a higher occurrence of false positive for Trisomy 21.

Key words: free beta-hCG, SLE, trisomy 21.

Table I. 1st Trimester markers in NAI populations and Groups of AI population (assembled by pathology) (**S21:05**)

Variable	NAI Population (n= 47925)	AI APS 8n=60)	AI Crosins Disease 8n=79)	AI MULT Sclerosis 8n=45)	AI AX 8n=53)	AI SLE 8n=51)	AI Ulcer Colitis	AI Others 8n=12)
Gestational Age at Examination, w. median (IQR)	12.72 (12.36-11.17)	12.55 (12.27-13.05)	12.74 (12.46-13.11)	12.61 (12.33-13.88)	12.66 (12.34-12.99)	12.61 (12.40-12.06)	12.7 (12.14-12.90)	12.57 (12.26-12.86)
CRL, mm, median (IQR)	65.5 (58.60-60.00)	61.2 (57.75-67.56)	63.7 (59.90-68.90)	62 (58.20-68.00)	62.7 (58.85-67.18)	61.9 (58.10-68.16)	63.1 (58.60-65.90)	63.4 (57.38-65.06)
NT, mm, median (IQR)	1.8 (1.68-2.10)	1.8 (1.12-2.80)	1.9 (1.60-2.10)	1.7 (1.50-2.10)	1.8 (1.60-2.10)	1.8 (1.58-2.06)	1.8 (1.50-2.20)	1.9 (1.70-2.10)
BIOCHEMICAL MARKERS								
PAPP-A, U/L, median (IQR)	2.83 (1.79-4.42)	2.19 (1.55-3.78)	2.56 (1.74-2.65)*	2.2 (1.29-2.25)	2.25 (1.37-3.49)	2.14 (1.34-4.86)	2.78 (1.65-4.82)	2.43 (1.72-3.87)*
PAPP-A, MoMs, median (IQR)	1.003 (0.6858-1.4262)	1.019 (0.6233-1.4468)	0.921 (2.6929-1.2234)	0.984 (0.3453-1.2587)	0.895 (0.4818-1.1958)	0.972 (0.5289-1.6883)	1.042 (0.7075-1.5282)	0.870 (0.7289-1.3676)
Free β-hCG, U/L, median (IQR)	36.5 (24.10-54.20)	31.2 (20.10-44.30)	42.24 (30.60-60.61)	39.5 (27.40-53.70)	44.8 (28.88-21.90)*	51.1 (29.30-79.16)*	40.7 (26.30-46.00)	38.37 (28.50-59.36)*
Free b-hCG, MoMs, median (IQR)	0.594 (0.6761-1.5862)	0.919 (0.5714-1.3967)	1.176 (0.8105-1.6335)	1.113 (0.6876-1.3965)*	1.130 (0.7983-2.0420)*	1.402 (0.3715-2.3859)*	1.024 (0.7228-2.3221)	0,996 (0.6862-1.4667)

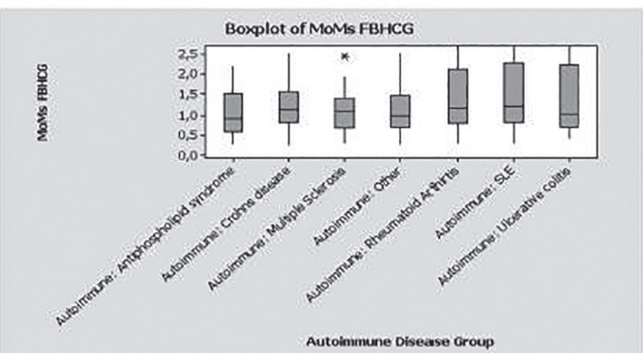
Table II. Analysis of detection rates in autoimmune populations.

Positive screening in Autoimmune population						
61			PPV	FPV	Excluded	FPR
0-50	25	40.98%	9	16	0	4.43%
50-100	9	14.75%	1	7	1	1.94%
100-150	11	18.03%	0	11	0	3.05%
150-200	5	8.20%	0	5	0	1.39%
200-300	11	18.03%	0	10	1	2.77%
Total	61	100.00%	10	49	2	13.57%

Table III. Analysis of Median MoMs FBHCG in NAI populations and Groups of AI Populations.

	Median MoMs FBHCG							
	NAI Population	AI-SLE Population	AI-AR Population	AI-MUST Sclear Population	AI-SAP Population	AI-Cronns Disease Population	AI-Ulcer Colitis Population	AI+ Others Population
RPN POS	1.726	2.554	1.968	0.736	1.376	2.416	1.997	1.056
Aneuploid (YP)	1.526	2.682	2.033	N/A	N/A	3.419	1.639	6.332
Euploid (FP)	1.721	2.124	1.968	0.736	1.376	2.416	2.109	1.543
RPN NEG	0.957	1.135	1.037	1.113	0.918	1.079	0.973	0.964
Aneuploid (FN)	0.288	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Euploid (VN)	0.958	1.135	1.037	1.113	0.918	1.101	0.973	0.864

Fig. 1. MoMs FBHCG in AI populations (assembled by pathology.



S21:06

PREGNANCY AND FETAL OUTCOME IN SLE PATIENTS: THE IMPORTANCE OF DISEASE REMISSION BEFORE CONCEPTION

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Objective. To explore if disease remission before conception can protect against flares in pregnant SLE patients and if SLE flares during pregnancy may affect health status of children.

Design and Method. We evaluated 78 pregnancies in 55 SLE subjects seen at our Unit between 2006 and 2015. The mean age at conception (±SD) was 32.9±4.5 years and the mean disease duration (±SD) 10.2±6.1 years.

We measured disease activity before (6 months) and during pregnancy with SLE Disease Activity Index-2000 (SLEDAI-2K) and SLE Pregnancy Disease Activity Index (SLE-P-DAI) scores, respectively. We defined SLE flare as a clinical increase in SLE-P-DAI score of at least 1 point compared with previous evaluation. Three levels of remission were defined using the SLEDAI-2K: complete remission (no disease activity in corticosteroid-free and immunosuppressant-free patients), clinical remission off corticosteroids (serologically active clinical quiescent [SACQ] disease in corticosteroid-free patients), and clinical remission on corticosteroids (SACQ disease in patients taking prednisone up to 5mg/day). Statistical analysis was performed using SPSS software for Windows (22.0, Chicago, IL).

Results. In our patients, the prominent manifestations during the disease course before pregnancy were arthritis (65.4%), skin manifestations (52.6%), hematological disorders (42.3%), glomerulonephritis (GLN) (35.9%), constitutional symptoms (27.3%), serositis (11.5%) and neurological involvement (6.4%). In the 6 months before conception, 16 patients (21.1%) were in complete remission, 26 (34.2%) in clinical remission off corticosteroids, 24 (31.6%) in clinical remission on corticosteroids, and 10 patients (13.2%) were unremitted.

Disease flares occurred in 19 out of 78 pregnancies (24.4%). Manifestations during flares were GLN (14.1%), skin rash (2.6%), hematological disorders (5.1%), arthritis and neurological involvement (1.3%).

SLE flares were significantly more common in unremitted than in remitted patients during the 6 months before conception: 80% vs 15.1% (p<0.001) without any difference among patients with different levels of remission. The frequency of preterm delivery was significantly higher in patients that flared during pregnancy than in those who did not flare: 42.1% vs 13.4% (p=0.009).

Finally, no differences in the risk of IUGR, fetal death, preeclampsia and spontaneous miscarriage were found between the two groups.

Conclusions. SLE remission in the 6 months before conception is protective against flares during pregnancy. SLE flares during pregnancy are predictors of preterm delivery.

Key words: SLE, pregnancy and fetal outcome, disease remission and flares

S22: Lupus pregnancy

S22:04

IN VITRO FERTILIZATION IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS OR ANTIPHOSPHOLIPID SYNDROME: A SERIES OF 97 PROCEDURES

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Objective. Data about complication and success rates for *in vitro* fertilization (IVF) of women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS) are sparse with only two series.
Design and Method. This retrospective study describes women with SLE and/or APS who had at least one IVF cycle between 1995 and 2014, in four internal medicine centres in France.
Results. 37 women with SLE (n=23, including 8 with antiphospholipid antibodies), SLE with APS (n=4), or primary APS (n=10) underwent 97 IVF.
Manifestations among the 27 women with SLE were articular (n=22), cutaneous (n=19), haematological (n=9), cardiac (n=5), renal (n=4), pulmonary (n=2), and neurological (n=1). None had chronic renal insufficiency. Among the 14 women with APS, clinical manifestations included obstetric complications (n=8), and/or venous (n=5) and arterial thromboses (n=2). In 43% of cases, the infertility was female in origin, for 19% male, 14% mixed, and 24% unexplained. No women had premature ovarian insufficiency due to cyclophosphamide.
Median age at IVF was 34 years (range: 26-46). The median number of IVF cycles was 2.6 (1-8). Women were treated with hydroxychloroquine (72%), steroids (70%), azathioprine (3%), aspirin (92%), and/or low-molecular-weight heparin (62%).
Ovulation induction protocols varied according to the centre. Agonist GnRH protocols were used in 50 procedures (51.5%), antagonist GnRH protocols in 15 (15.5%), retrieval took place during natural or substituted cycles in 24 (25%), and the precise procedure was unknown in 8 (8%). Oocyte donation was used for 15 procedures (15.5%). For 63 of the 65 IVF procedures in women with SLE (97%), the patients had had no moderate flares for at least 6 months and no severe flares for a year. None of the women with APS had had a thrombosis in the year before IVF. 93 of the IVF cycles (96%) were considered appropriate and supervised by an internist.
Complications occurred in or after 8 IVF cycles (8%): SLE flares in 4 IVF (performed in 3 women, with polyarthritis in 3 IVF and lupus enteritis in 1) and thromboembolic events in 4 others (also in 3 women, with lumbo-ovarian thrombosis (n=1), distal deep venous thrombosis (n=2), and a distal pulmonary embolism (n=1)). One SLE flare was the first sign of previously undiagnosed SLE (polyarthritis). Poor treatment adherence explained 2 flares and 2 thromboses. No ovarian hyperstimulation syndrome was reported.
There were 27 (28%) pregnancies, 23 live births with 26 neonates (3 twin pregnancies), 2 miscarriages, and 2 terminations for trisomy 13 and 21. Six spontaneous pregnancies occurred during the follow-up. Finally, 26 women (70%) delivered at least one healthy child.
Conclusions. These preliminary results confirm that IVF can be safely and successfully performed in women with SLE and/or APS who are in remission and receiving adequate treatment.

Key words: *in vitro* fertilization, systemic lupus, antiphospholipid syndrome

S22:05

COUNSELING ON FAMILY PLANNING AND CONTRACEPTION IN PATIENTS WITH RHEUMATIC DISEASES: ANALYSIS OF 324 PATIENT-REPORTED QUESTIONNAIRES FROM A MULTICENTER ITALIAN STUDY

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Objective. Rheumatic diseases (RD) often affect young women in reproductive age, so that pregnancy, contraceptive methods and family planning are crucial for the quality of life of these patients. We aimed to investigate 'women health', through a self-reported questionnaire. Answers from patients with Systemic Lupus Erythematosus/Antiphospholipid Syndrome (SLE/APS) vs. Rheumatoid Arthritis (RA) were compared.
Methods. 24 Italian participating centers distributed a self-reported questionnaire (65 multiple-choice and 12 open-answer questions) to women with RD (18-55 years).
Results. Answers were collected 161 SLE/APS and 163 RA; the mean age at diagnosis was 29 and 31 respectively. Patients that did not want to have children before and after the diagnosis (5 and 9 respectively) and who had all the children before the diagnosis (17 and 37 respectively) were excluded. We then analyzed 139 SLE/APS vs. 117 RA.
Nearly 50% of all patients declared that RD influenced their desire to have children: half of them reduced the number of children they wanted (Table 1). 24% SLE/APS vs. 13% RA had at least one miscarriage.
29% SLE/APS and 34% RA were never asked by their Rheumatologist about the desire to have children. 60 vs. 70% received a counseling about contraception, given by a gynecologist (52% vs. 64%), rheumatologist (26% vs. 14%), or from both (9% in both groups).
68% from both groups received a counseling before pregnancy: 51% vs. 50% of them from both rheumatologist and gynecologists, 16% vs. 22% only by Rheumatologist. The counseling changed positively the family planning in 73% and 58% respectively.

Table I. Reasons for the reduced family size in patients interviewed, who declared that their RD have influenced their desire of having children (SLE/APS=69 vs. RA=56).

The disease has reduced your desire to have children?	SLE/APS	RA
NO	28/69 (41%)	22/56 (39%)
YES	**38/69 (55%)**	**29/56 (52%)**
No Answer	3/69 (4%)	5/56 (9%)
If yes, I reduced the number of children that I wanted, because I was afraid...	**SLE/APS**	**RA**
...of not being able to take care of them because of the RD	**18/69 (26%)**	**22/56 (39%)**
...that the child could have the same RD	**9/69 (13%)**	**9/56 (16%)**
...that drugs or disease could harm the baby	**17/69 (25%)**	**21/56 (38%)**

Conclusions. SLE has a major impact on reproductive planning and restriction of family size, possibly mediated by an increased rate of miscarriages as compared to RA patients. The concerns about reproductive issues could be positively overcome by adequate counseling.
Rheumatologists should implement the discussion about family planning in the management of young women with RD, especially in SLE/APS patients in whom contraception and pregnancy have particular implications.

Key words: questionnaire, counseling, family planning.

S23: Joint and skin in SLE

S23:04

PREDICTORS OF MUSCULOSKELETAL FLARES AND JACCOUD'S ARTHROPATHY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A 5-YEAR PROSPECTIVE STUDY

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Objective. Identifying factors associated with musculoskeletal (MS) flares and development of joint damage, such as deformities, would help preventing a major cause of disability for patients with Systemic Lupus Erythematosus (SLE). In particular, unveiling the progression and predictive values of synovitis, tenosynovitis and erosions detected by high-resolution ultrasound (US), can be crucial in facilitating targeted therapies and measuring response. Our aim was to investigate the prognostic value of US in predicting musculoskeletal flares and Jaccoud's arthropathy (JA) in SLE.
Design and Method. Eighty out of 94 patients (76 female; age 45.5±13.2 years) with non-deforming non-erosive (NDNE) arthritis and 48/60 healthy controls (42 female; age 49.6±11.6 years) completed a 5-year follow-up study. Each patient was prospectively assessed for the occurrence of musculoskeletal flares using BILAG2004 and hand deformities according to Jaccoud's articular index. Baseline clinical, serological, semi-quantitative (0 – 3 scale) ultrasound (US) findings, PD-synovitis score (sum of all PD-signal on targeted joints) and PD-tenosynovitis score (sum of all PD-signal on targeted tendons) were used as covariates for univariate and multivariate analyis to identify predictors for study outcomes. Short Form 36 v2 (SF36v2) health survey questionnaire was administered to evaluate the health related Quality of Life.
Results. Twelve MS flares in 10 (12.5%) patients were recorded and the incidence rate was 3.0 per 100 patient-year. Baseline PD-synovitis score independently predicted MS flare (p<0.001; RR 2.0; 95% CI 1.4 – 3.0) within 2 years since US examination. Baseline PD-synovitis score >2 was associated with a 2-year risk of MS flare (sensitivity 66.7%; specificity: 97.3%; AUC=0.804; 95%CI 0.699 – 0.886). Five (6.2%) patients developed JA whose incidence rate was 1.25 per 100 patient-year. Independent risk factors for development of JA were higher longitudinal BILAG score in the musculoskeletal domain (p=0.005; RR 2.4 95% CI 1.3 - 4.6) and longer disease duration (p=0.013; RR 1.2; 95% CI 1.1-1.3). JA and active musculoskeletal inflammation (MS-BILAG>=C), but not US erosions, were associated with lower results in SF36v2 physical and mental summary components.
Conclusions. Performing musculoskeletal US can be useful in order to predict MS flares. Jaccoud's deformities may arise in patients with long-standing SLE and prolonged, even subclinical, joint and tendon inflammation.

Key words: arthritis, Jaccoud's arthropathy, high-resolution ultrasound

S23:05

PREVALENCE OF ANTI-CARBAMILATED PROTEINS ANTIBODIES IN A COHORT OF SLE PATIENTS WITH JOINT INVOLVEMENT

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Objective. Joint involvement is a frequent manifestation in patients affected by Systemic Lupus Erythematosus (SLE) occurring up to 90%. Moving from the similarities between the joint involvement in SLE and in Rheumatoid Arthritis (RA) patients, several studies have evaluated the prevalence of RA-related autoantibodies in SLE. Anti-citrullinated proteins antibodies (ACPA) show a frequency ranging from 4.4% to 27.3%; rheumatoid factor (RF) ranges from 17 to 45.4%. Recently, anti-carbamilated proteins antibodies (anti-CarP) have been suggested as a new biomarker for RA and they can be detected in about 16% of seronegative RA patients. No data are available concerning the frequency of these autoantibodies in SLE patients. The aim of the present study was to detect the prevalence of RA-related autoantibodies in SLE patients with joint involvement and the associations with clinical and laboratory features.
Design and Method. SLE patients (ACR criteria of 1997) with a clinical history of joint involvement (arthralgia or arthritis) were evaluated. Clinical and laboratory data were collected in a standardized computerized electronically filled

form. Arthritis patients were further sub-grouped in those with non-deforming arthritis (NDA) and those with Jaccoud arthropathy (JA). All patients underwent blood draws to detect RF and ACPA by using the commercial ELISA kit and anti-CarP by home-made ELISA. Results were expressed in IU/ml and values above 340 IU/ml were considered positive.
Results. Seventy-eight SLE patients were evaluated (F/M 73/5; mean±SD age 47.6±11.2; mean±SD disease duration 214.3±115.6 months). The prevalence of RF, ACPA and anti-CarP was 61.5%, 46.1% and 19.2%, respectively. Four patients were positive for all antibodies: 75% of these were JA patients. RF was significantly more frequent in patients with arthralgia compared with arthritis patients (76.5% vs 57.4%, *p*=0.006). Concerning ACPA and anti-CarP, no differences between arthralgia and arthritis patients were identified (11.8% vs 21.3% and 52.9% vs 42.6% respectively; *p*=NS). Regarding arthritis patients, anti-CarP were significantly more frequent in patients with NDA than JA patients (48.8% vs 27.8%, *p*=0.003). The mean±SD titre of anti-CarP antibodies was higher in NDA patients than those with arthralgia and JA, without a significant difference (561±853.1 IU/ml vs 530±418.8 IU/ml and 448±580.8 IU/ml, respectively; *p*=NS). Notably, anti-CarP were identified in 45% of double negative (ACPA-/RF-) patients, with a mean±SD titre of 963.3±1348.9 IU/ml. No significant associations between RA-related autoantibodies and clinical and laboratory features have been identified.
Conclusions. In the present study, we evaluated for the first time the prevalence of anti-CarP in SLE patients with joint involvement, identifying a prevalence higher than 40%. Notably, these autoantibodies seem to be associated to NDA. Anti-CarP were positive in almost half of ACPA-/RF- patients, a higher percentage compared with data about seronegative RA. Further investigations on larger cohorts are necessary to better understand the possible role of anti-CarP as biomarker in SLE joint involvement.

Key words: systemic lupus erythematosus, anti-CarP antibodies, joint involvement

S23:06

SAFETY PROFILE AND CAUSE OF DISCONTINUATION OF ANTIMALARIALS IN A MONOCENTRIC COHORT OF PATIENTS WITH SYSTEMIC AND DISCOID LUPUS ERYTHEMATOSUS

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Objective. Antimalarials are among the most used drugs for Discoid Lupus Erythematosus (DLE) and Systemic Lupus Erythematous (SLE), thanks to their additional effects beyond immunomodulation and a good tolerability profile. Aim of the study was to determine safety and reasons of discontinuation of antimalarials in DLE and SLE patients, focusing on ophthalmological alterations.
Design and Method. Consecutive patients who are prospectively followed up at our Lupus Clinic were asked about chloroquine (CQ) or hydroxychloroquine (HCQ): treatment duration, causes of temporary or definitive discontinuation, ophthalmological screening and emergence of maculopathy.
Results. Among the 845 patients of our Lupus cohort, 59% (505 patients, F=452, M=52; mean age 45.6±12.4 years; mean disease duration 141.9±104.6 months) was treated with CQ or HCQ; 402 of them have a diagnosis of SLE, 103 of DLE. Mean follow-up was 50.4±46.1 months. Of the 505 patients, 1.4% received CQ, 88.3% HCQ and 10.3% used both antimalarials in the course of medical history, with a mean therapy duration of 82.5±77.4 months.
Safety analysis showed that 19.4% of patients experienced at least one side effect during the antimalarial therapy and this occurrence was responsible for the need for temporary or permanent suspension in 9.1% and 10.3% of cases respectively; 19.3% of patients experienced side effects during the therapy with HCQ and 8.6% during CQ. Fifty-one patients switched from CQ to HCQ because of tolerability. The prevalence of side effects was significantly higher in patients treated with HCQ than in those treated with CQ (19.3% vs 8.6%, *p*=0.046), but the percentage of patients that definitely withdrew the antimalarial was approximately the same in both groups (about 15%). In 55.1% of cases, the adverse event was mild or moderate. Ophthalmological alterations were reported by 8.5% but were confirmed by the ophthalmological examination only in 5.5% of cases. Over the course of the follow-up, 8.5% (43/505) of patients definitely discontinued the antimalarial for retinal toxicity; 53.5% of them (23 patients) temporarily discontinued the treatment for reversible ophthalmological manifestations due to the therapy or for temporary visual disturbances reported by the patients themselves. Ophthalmological alterations were associated to age of the patients (*p*=0.039), duration of disease (*p*=0.06) and duration of the antimalarial therapy (*p*=0.02), but not to CQ nor HCQ dose, comorbidity (hypertension [*p*=0.7], diabetes mellitus [*p*=0.9] and renal failure [*p*=0.3]) and lupus nephritis (*p*=0.2).
Conclusions. This longitudinal study on the largest monocentric cohort described to date confirmed the good safety profile of antimalarials in DLE and SLE patients. The most severe adverse effect associated with the antimalarial therapy - the maculopathy - affected a low percentage of patients; however, it should be kept in mind that ocular toxicity is the main cause of permanent discontinuation of HCQ and CQ.

Key words: antimalarials, safety, ophthalmopathy

S24: Outcome, costs and comorbidities in SLE

S24:04

OVERALL CAUSE AND CAUSE SPECIFIC MORTALITY IN A MULTINATIONAL INCEPTION COHORT OF SLE

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Objective. A large multicenter multinational inception cohort was established initially to study risk factors for atherosclerosis (AS) in SLE. The aim of this study was to determine all cause and cause-specific mortality and their risk factors during the first 10 years of observation.
Design and Method. Patients enter the cohort within 15 months of SLE diagnosis (>/=4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Deaths are recorded as they occur and the cause of death was coded according to ICD9. Overall and Cause-Specific Survival curves were obtained using a Cumulative Incidence Competing Risk Analysis. Prediction models for overall survival and cause-specific for the three major causes were done using time-dependent covariate analysis for competing risks using date of birth as time zero. Variables included were geography of origin, ethnicity, sex, disease duration, disease activity, damage and medication use. The selection of variable retained was done using the stepwise approach.
Results. 1677 patients had follow-up beyond enrolment. At the time of data cut 78 patients had died. Cause of death included: atherosclerosis 11, active SLE 17, infection 27 and all other causes 23 (cancer in 5, other in 8, and unknown in 10). At enrolment 89.0% were female with a mean age at diagnosis of 34.9±13.4 yrs and a disease duration of 0.5±0.4 yrs. Mean SLEDAI-2K was 5.4±5.4, SDI 0.12±0.50 (SDI >0: 131 (7.9%)). Patients on steroids 1167 (69.8%), on antimalarials 1124 (67.3%) and on immunosuppressives 671 (40.2%). 825 (49.2%) were Caucasian, 275 (16.4%) Black, 260 (15.5%) Hispanic, 255 (15.2%) Asian and 61 (3.6%) other. Geography of origin included USA 460 (27.4%), Canada 398 (23.7%), Europe 450 (26.8%), Mexico 160 (9.5%), and Asia 209 (12.5%). The Competing –Risk survival Analysis is presented in the Table.

	Hazard Ratio	95% Confidence Interval	P value
ALL CAUSES			
Mexico	4.02	2.30, 7.02	<0.0001
Disease Duration	0.90	0.82, 0.98	0.02
SDI	1.47	1.29, 1.66	<0.0001
On Steroids at Visit	3.97	2.01, 7.82	<0.0001
On Antimalarials at Visit	0.56	0.35, 0.89	0.01
ATHEROSCLEROSIS			
SDI excluding cardiac damage	1.56	1.17, 2.06	0.002
ACTIVE LUPUS			
Mexico	9.73	3.31, 28.59	<0.0001
Sex Male	4.40	1.51, 12.82	0.007
Disease Duration	0.70	0.55, 0.91	0.006
SDI	1.58	1.17, 2.13	0.003
INFECTION			
Hispanic	4.50	1.70, 11.92	0.002
SDI	1.59	1.32, 1.93	<0.0001
On Steroids at Visit	25.27	3.35, 190.66	0.002
On Antimalarials at Visit	0.39	0.17, 0.92	0.03
On Immunosuppressives at Visit	0.27	0.12, 0.61	0.002

Damage was an important risk factor for all cause and cause-specific mortality. Demographic factors, disease activity and treatment contribute differently to mortality both all cause and cause specific. Anti-malarials are protective for all-cause mortality and mortality due to infection.
Conclusions: Risk factors differ for all cause mortality and mortality related to active lupus, atherosclerosis and infection and all must be considered in pursuing preventive strategies.

Key words: SLE, mortality

S24:05

DOES THE SLICC DAMAGE INDEX UNDERESTIMATE COMORBIDITY-ASSOCIATED IMPACT ON THE SURVIVAL OF ELDERLY SLE PATIENTS?

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Objective. The SLICC Damage Index (SDI) is a predictor of survival of patients with Systemic Lupus Erythematosus (SLE). However, the SDI only scores damage that occurred after the SLE diagnosis and does not account for increased mortality risk due to other comorbidities.
The aim of this work is to investigate whether the SDI underestimates impact of comorbidities on survival of elderly SLE patients.
Design and Method. Patients with SLE fulfilling the SLICC'12 classification criteria and aged >=50 years from a single tertiary lupus clinic were included in this cross-sectional study. For each patient we scored the Charlson Comorbidity Index (CCI) and the SDI at time of last visit. The ten-year-survival probability was estimated for each patient applying the CCI. Association of the SDI and CCI scores was analysed with Spearman correlation. We compared the CCI scores in the group of patients with and without damage in the SDI (SDI=0 and SDI>=1) applying the Mann-Whitney U test. Statistical significance was considered if $p<0.05$.
Results. We included 81 SLE patients [77.8% female; median age - 68 years, interquartile range (IQR) 63.5-73.5; median SLE duration – 15 years, IQR 7.0-25.0]. From these patients, 75.3% presented a SDI score >=1. Score in the SDI and CCI was moderately correlated (rho=0.427, $p=0.0003$). In the group of patients without SDI damage, 66.6% presented comorbidities scored in the CCI. CCI score was higher in the group with SDI >=1 ($p=0.012$). Estimated median 10-year survival probability was 53.4% and 21.4% for the group with SDI=0 and >=1, respectively ($p=0.013$).
Conclusions. Many patients without SDI damage present comorbidities associated with higher estimated risk of mortality according to the CCI. The SDI may underestimate comorbidities with impact on survival.

Key words: SLICC Damage Index, comorbidity, Charlson Comorbidity Index

S24:06

LONG-TERM OUTCOMES OF CHINESE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A SINGLE-CENTER COHORT STUDY

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Objective. This study aims to exhibit the prognosis, both mortality and morbidity, for patients with Systemic Lupus Erythematosus (SLE) in a large single-center cohort in China.

Figure 1 Kaplan-Meier survival curves in SLE patients with and without SDI ≥1

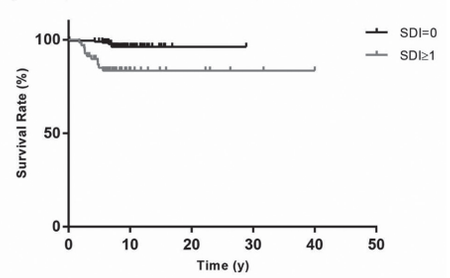

Table 1 Independent risk factors for mortality by Cox Regression analysis

	HR	95% CI	p value
Age at onset	0.993	0.943-1.045	0.789
Male gender	1.128	0.251-5.080	0.875
Time from onset to diagnosis > 1 year	6.129	1.934-19.428	0.002
Disease duration	0.895	0.784-1.023	0.104
Renal involvement	2.100	0.599-7.358	0.246
Hematologic involvement	1.675	0.495-5.669	0.407
Neuropsychiatric involvement	4.522	1.518-13.471	0.007
Gastrointestinal involvement	6.496	1.107-38.112	0.038
Pulmonary involvement	1.790	0.321-9.971	0.506
Organ damage	6.898	2.008-23.697	0.002

Design and Method. A cohort of Chinese SLE patients were recruited from April 2009 to February 2010, and followed up regularly at clinic. Data for baseline, follow-up and survival were collected, including demography, manifestations, activity (SLEDAI-2K), SLE International Collaborating Clinics Damage Index (SDI), and medications. Kaplan-Meier method was adopted for survival analysis. Predicting factors for mortality were evaluated by COX proportional hazard model.
Results. A total of 260 patients (female: male=237:23) were included, with a mean age as 31.97±11.70 and 3.02±4.91 years of disease duration at baseline. The 1-year, 3-year and 5-year survival rates from diagnosis were 99.2%, 97.3% and 95.4% respectively. At entry, 35 patients had organ damage and it increased to 68 patients after 6 years. Of all damages, the most frequent one was musculoskeletal (27.6%). Cox regression indicated that organ damage, neuropsychiatric involvement, gastrointestinal involvement and more time from onset to diagnosis are predictors for all-cause mortality.
Conclusions. Long-term survival rates in our cohort are comparable to previous reported ones for both Chinese and Caucasians. For Chinese SLE patients, organ damage, neuropsychiatric involvement, gastrointestinal involvement and time from onset to diagnosis are prognostic factors and deserve more attention in the future.

Key words: systemic lupus erythematosus, survival, organ damage

S25: Challenges in the management of APS

S25:03

DIFFERENTIATION BETWEEN APS PATIENTS AND ANTIPHOSPHOLIPID ANTIBODY-POSITIVE CARRIERS – IMPOSSIBLE OR MATTER OF TECHNIQUE?

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Objective. Purpose: For the analysis of antiphospholipid antibodies (aPL) being the hallmark in the serology of the antiphospholipid syndrome (APS), enzyme-linked immunosorbent assays (ELISAs) have been proposed by consensus guidelines. However, they can detect aPL in apparently healthy subjects (HS), so called aPL-positive (aPL+) asymptomatic carriers, and infectious disease patients. A novel line immunoassay (LIA) for the multiplex analysis of aPL was developed to address this challenge.
Design and Method. Methods: Sixty-one APS patients (34 primary, 5 secondary, 22 obstetric APS), 146 controls including 24 aPL+ asymptomatic carriers and 73 infectious disease controls (IDC) were analyzed using a novel multiplex line immunoassay (LIA) for the detection of aPL to cardiolipin (CL), phosphatic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, beta2-glycoprotein I (β2GPI), prothrombin, and annexin V for aPL reactivity. Samples have been also tested by routine anti-CL and anti-β2GPI ELISAs and Lupus Anticoagulant assay as well as anti-β2GPI Domain 1 and 4-5 assays.
Conclusions. Comparison of LIA with the consensus aPL assays revealed good agreement for IgG/IgM anti-β2GPI and anti-CL by Cohen's kappa statistics. Anti-CL and anti-β2GPI IgG/IgM reactivity by LIA was significantly higher in APS patients vs. HS and IDC as detected by ELISA. IgG binding to CL and β2GPI in LIA was significantly lower in aPL+ carriers and VDRL+ samples than in APS patients. Human monoclonal antibodies against domain 1 recognized β2GPI bound to LIA-matrix and in anionic PL-complexes. The novel LIA appears to favor the detection of anti-β2GPI Domain 1 antibodies.

Key words: antiphospholipid syndrome, antiphospholipid antibody, line immunoassay

S25:04

THROMBOSPONDIN-1 IS ELEVATED IN THE PLASMA OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME. IMPLICATIONS IN THE PATHOGENESIS OF ANTIPHISPHOLIPID SYNDROME

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Objective. Antiphospholipid syndrome (APS) is an acquired thombophillia characterized by recurrent thromboembolism andpregnancy morbidity. Thrombospondin (TSP-1) is a matricellular glycoprotein secreted by platelets upon activation with proinflammatory,
antiangiogenic and proapoptotic properties. TSP-1 activates TGF-b1 and has been shown to be involved in TH-17 response. We aimed to investigate the role of Thrombospondin-1 in APS.
Design and Method. The study involved 90 patients with APS, 46 healthy controls (HC) and 26 SLE patients. Plasma, serum, and total IgG were isolated from all groups. Monocytes and $CD4^+$ T-cells were isolated from 4 HC. Human Umbilical Vein Endothelial Cells were isolated from 2 APS patients and 5 HC and cultured with plasma or total IgG from HC or APS patients. Monocytes were stimulated with total IgG and these supernatants were used to stimulate $CD4^+$ T-cells. Plasma and cell culture supernatant TSP-1, IL-1b, IL-17A and free active TGF-b1 levels were determined using an ELISA.
Results. APS patients had higher plasma levels of TSP-1 than HCs and SLE patients (APS: mean 390ng/ml vs HC: 144.3 vs SLE: 153.0 $p<0.0001$)
Patient plasma free active TGF-b1 levels were higher and strongly correlated with TSP-1 (r =0,827 and $p<0,0001$).

APS HUVECs and HC HUVECs cultured with APS plasma expressed higher levels of TSP-1 than those cultured with HC plasma. (APS=139.4ng/ml vs HC=22.8ng/ml p=0,0009). Monocytes stimulated with APS total IgG produced higher levels of IL-1b and TSP-1 compared to the ones stimulated with HC IgG (700pg/ml vs 50pg/ml and 500ng/ml vs 200ng/ml respectively). APS stimulated supernatants induced the expression of IL-17A from T-cells (250pg/ml) whereas the HC had no effect.
Regarding the clinical aspects of APS, there was significant difference between the patients with pregnancy morbidity alone (130.1ng/ml) and those with miscarriages and thrombosis (403.2ng/ml).
Conclusions. Preliminary results suggest that APS patients have higher TSP-1 plasma levels which correlate with free active TGF-b1. Monocytes and HUVECs treated with APS plasma and APS IgG produce higher levels of TSP-1 and IL-1b and these supernatants induce the expression of IL-17A from naïve T-cells.
All these suggest a possible involvement of TSP-1 in thrombus formation, inflammation and inhibition of angiogenesis that needs further study.

Key words: APL, IL1, IL17

S25:05

UTILITY OF ANTI-BETA2GLYCOPROTEIN I IGA AND ANTI-DOMAIN 1 AS A RISK FACTOR FOR RECURRENT THROMBOSIS IN PRIMARY ANTIPHOSPHOLIPID SYNDROME

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Objective. Actual consensus in Antiphospholipid Syndrome (APS) management includes the evaluation of inherited and acquired risk factors. It has been suggested that they play a role as triggers to pathogenic antiphospholipid antibodies (aPL) in association with aPL profile. IgA antiBeta2Glycoprotein I (a-B2GPI), anti-phosphatidylserine/prothrombin (a-PS/PT) IgG/IgM and anti Domain 1 (a-D1) antibodies ar not currently recognized as formal laboratory criteria for the APS. However, there are experimental data showing their pathogenic role.
Design and Method. We evaluated a retrospective and monocentric cohort of patients with thrombotic Primary Antiphospholipid Syndrome (PAPS) according to the updated Sapporo Criteria, all positive for anti-Beta2Glycoprotein I IgG antibodies (a-B2GPI) at home-made validated ELISA test. aB2GPI IgA/IgM, a-PS/PT IgG/IgM and a-D1 IgG antibodies were tested with BIOFLASH (QUANTA Flash, INOVA Diagnostics Inc.). We correlated the antibody positivity with type of thrombotic event (arterial-A, venous-V) and number of events (singular-S or recurrent-R). Chi square test was used to compare categorical variables.
Results. The study included 87 PAPS patients (65 female, mean age 50 years; patients with recurrent events: 31, patients with single event: 56; patients with venous event: 59, patients with arterial event: 18, patients with venous and arterial events-V+A: 10). Hypertension and hypercholesterolemia were associated to the first A event (64.0% vs 20.6% p<0.0001; 46.0 % vs 21.6% p=0.002). The interruption of therapy was the most frequent identified trigger for each thrombotic event (15.5%), followed by pregnancy (5.2%) and puerperium (3.4%). No trigger could be recognized in the majority of recurrences (70.7%). During the follow-up (mean 120.7 months) we observed 41 recurrences in 31 patients. The switch from venous to arterial events was found in 7 patients and the opposite in 3. Recurrent events were significantly associated with aB2GPI IgA positivity (65% vs 39%, p<0.05). Positivity for aD1 antibodies was associated with V events (84% vs 32%, p=0.05) while PS/PT IgG with recurrent A+V events (35% vs 18%, p<0.03). Double positivity for aB2GPI IgA and aD1 were very significantly associated with overall thrombosis (p=0.002), in particular with V (p=0.007).
Conclusions. Patients with PAPS still develop significant recurrence of thrombosis despite treatment (35.6%). Besides traditional cardiovascular risk factors, complete aPL profile should be included in the risk stratification, being, among patients with positivity for a-B2GPI IgG, aB2GPI IgA and a-D1 positive patients respectively at higher risk of recurrent and venous thrombosis.

Key words: thrombosis risk stratification, anti Beta2Glycoprotein I IgA, anti domain 1 antibodies

S25:06

ANTIPHOSPHATIDYLSERINE/PROTHROMBIN ANTIBODIES AS A RISK FACTOR OF DISEASE SEVERITY IN PRIMARY ANTIPHOSPHOLIPID SYNDROME

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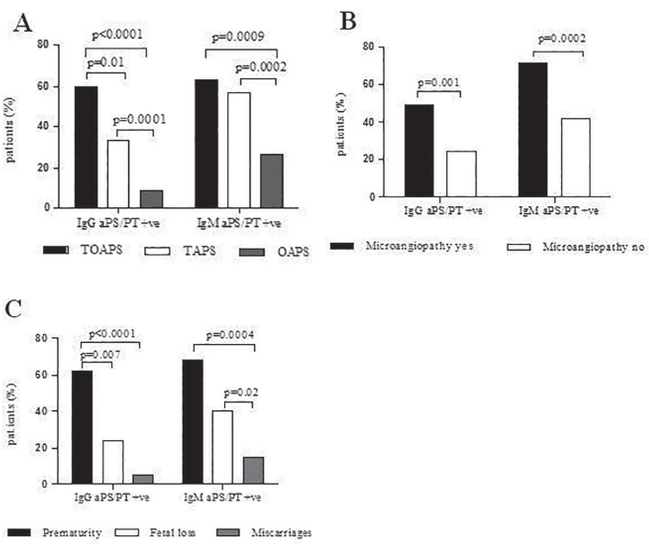
Objective. Anti-phosphatidylserine/prothrombin complex (aPS/PT) antibodies (abs) are emerging as a relevant biomarker for antiphospholipid syndrome (APS). Recently, we have demonstrated their association with clinical features of APS and lupus anticoagulant activity. Furthermore, we argued aPS/PT clinical relevance in primary APS (PAPS) by comparing their performance with that of conventional antiphospholipid antibodies in PAPS patients. We aimed now to explore the role of aPS/PT abs as a risk factor of severity in APS.



Design and Method. We considered 197 primary APS patients and 206 controls (106 patients with autoimmune diseases and 100 healthy blood donors). IgG/IgM aPS/PT were detected using a commercial ELISA kits INOVA Diagnostics, Inc. (San Diego, California, USA). The cut-off was calculated as 99th percentile of 100 healthy blood donors.
Results. The sensitivity of IgG aPS/PT and IgM aPS/PT abs was 30% and 48.2% respectively; while the specificity was 97.6% and 97%, respectively. IgG aPS/PT abs were significantly prevalent in patients with both thrombosis and pregnancy morbidity (TOAPS) than in those with thrombosis (TAPS) or pregnancy morbidity (OAPS) alone and in TAPS patients with respect to OAPS one (Figure 1A). IgM aPS/PT abs were significantly prevalent both in TOAPS and TAPS than in OAPS patients (Figure 1A). Also, the IgG and IgM levels were significantly higher in patients with TOAPS than in those with TAPS or OAPS alone (p<0.0001 and p=0.0008, respectively). IgG aPS/PT but not IgM aPS/PT were associated with the presence of both arterial and venous thrombosis compared to single thrombosis (p=0.004). While, both IgG and IgM aPS/PT were significantly associated with microangiopathy (Figure 1B). Also, their levels were significantly higher in patients with microangiopathy with respect to those without microangiopathy (p=0.0004 and p=0.0002, respectively). Finally, both IgG and IgM aPS/PT abs were significantly associated with prematurity with severe maternal complications (Figure 1C), and their levels, as well, reflect their prevalence (p=0.0001 for both).
Conclusions. According to these findings aPS/PT abs might be considered as a risk factor of disease severity for APS.

Key words: antiprothrombin antibodies, lupus anticoagulant, thrombosis

S26: Old and new clinical and pathogenetic challenges in SLE

S26:03

ADHERENCE TO HYDROXYCHLOROQUINE AS ASSESSED BY MEASUREMENTS OF DRUG AND METABOLITE BLOOD LEVELS IN AN INTERNATIONAL PROSPECTIVE STUDY OF SLE PATIENTS IN FLARE

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Objective. Non-adherence to treatment, a major cause of continued lupus activity and flares, may be difficult to recognize. In this international prospective study, we evaluated adherence to hydroxychloroquine (HCQ) in systemic lupus erythematosus (SLE) patients with flares (ClinicalTrials.gov: NCT01509989).
Design and Method. This study included 305 SLE patients (who all met the SLICC criteria) from 19 centres in 10 countries, all of whom had been prescribed HCQ for at least 2 months and were having a disease flare defined according to the SELENA-SLEDAI Flare Index. Adherence to HCQ was assessed by self-questionnaires (MASRI and Morisky), physician's assessment (VAS 0-100), and blood concentrations of HCQ and its main metabolite desethylchloroquine ([HCQ] and [DCQ]). Non-adherence was defined by MASRI <80%, Morisky<6, [HCQ] <200ng/ml and/or undetectable [DCQ].
Results. 305 patients (288 women; mean age 38±12ys) met the inclusion criteria. The median SLE duration was 11ys [range 1-46]; 108 patients (35%) had a history of lupus nephritis.
At enrollment, the median SELENA-SLEDAI score was 8 [2-30] and the flare was considered severe in 43%. The HCQ dosage was 400mg/d in 72%, 200mg/d in 15%, or another dosage in 13%. The median [HCQ] was 718ng/ml [0-4345] (1 missing data). In addition, steroids were prescribed in 76%, and immunosuppressives in 46%.
Severe non-adherence defined by [HCQ] <200ng/ml was found in 44 patients (14.4%). Twelve additional patients with very low median [HCQ] of 235ng/ml [210-343] had an undetectable concentration of DCQ indicating a very recent resumption of treatment. Thus, 56 patients (18.4%) were objectively defined as severely non-adherent.
The treating physician believed that 75% of these non-adherent patients were taking at least 50% of their prescribed HCQ dose, strongly suggesting that doctors were often unaware of non-adherence. The median VAS evaluating the adherence from the doctor's point of view was 75 [0-98] in objectively non-adherent patients vs 87 [0-100] in other patients. The doctor's opinion, therefore, was poorly informative.
Good adherence to treatment with HCQ (defined as MASRI >= 80%) was self-reported by 77% of the patients, including by 43% of those objectively severely non-adherent.
On the other hand, the investigators felt that only 12% of patients took less than 50% of HCQ, with severe non-adherence confirmed in 39%.
Non-adherent patients defined by self-questionnaires (MASRI<80% or Morisky <6) and/or drug blood levels, represented 47% of this cohort.
Conclusions. These data demonstrate that blood HCQ and DCQ measurements objectively identify significant non-adherence to HCQ in nearly 20% of SLE patients, with DCQ levels able to identify recent resumption of treatment. Non-adherence was often unrecognized by the doctor, suggesting usefulness of blood assays to more accurately determine adherence.

Key words: systemic lupus erythematosus, hydroxychloroquine, adherence

S26:04

STUDY OF ANTI-APOLIPOPROTEIN A-I ANTIBODIES AND PARAOXONASE 1 ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS; CORRELATION WITH DISEASE ACTIVITY AND DAMAGE INDICES

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Objective. To assess two novel risk factors of atherosclerosis in Systemic lupus erythematosus (SLE) patients; Paraoxonase 1 (PON1) activity, and anti-apolipoprotein A-I antibody (anti-Apo A-I) levels, in order to elucidate any possible correlation between both of them, and to demonstrate their relations to disease activity disease activity as well as disease related damage.
Design and Method. Forty SLE female patients and 40 apparently healthy volunteers were included in this study. Anti-Apo A-I antibody levels and PON1 activity levels were assessed. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaboration Clinics (SLICC)/ American College of Rheumatology (ACR) damage index were preformed to all patients.
Results. Compared with controls, SLE patients showed significantly lower PON1 activity and significantly higher titers of anti Apo A-I. Anti-Apo A-I antibody titers correlated inversely with PON1 activity. Elevated titers of anti-Apo A-I antibody and reduced PON1 activity were related to increased SLEDAI and (SLICC/ACR) damage index scores.
Conclusions. There is a decreased PON1 activity and formation of anti-Apo A-I antibodies in SLE patients and both of them correlated with disease activity as well as disease-related damage. PON1 activity and anti-Apo A-I antibodies might be involved in the pathogenesis of premature atherosclerosis in SLE patients.

Key words: systemic lupus erythematosus, anti-apolipoprotein antibodies, paraoxonase 1 (PON1).

S26:05

INTERFERON REGULATORY FACTOR 5 PROMOTES DISEASE IN THE FCGAMMARIIB-/- MOUSE MODEL OF LUPUS THROUGH TLR7-DEPENDENT AND -INDEPENDENT PATHWAYS

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Objective. Polymorphisms in interferon regulatory factor 5 (IRF5) are strongly associated with an increased risk of developing systemic lupus erythematosus. We previously demonstrated that IRF5 is required for disease development in the FcgammaRIIB-/- lupus mouse model. The exact pathways through which IRF5 acts to promote disease in this model are not known. As IRF5 plays a central role in signaling through TLR7, a TLR involved in pathogenesis in other lupus models, we investigated the relative effects of TLR7 deficiency, and combined TLR7 and IRF5 deficiency in the FcgammaRIIB-/- mouse model.
Design and Method. We generated the following experimental groups of FcgammaRIIB-/- female mice: TLR7+/+IRF5+/+ mice, TLR7+/+IRF5-/- mice, TLR7-/-IRF5+/+ mice and TLR7-/-IRF5-/- mice. Mice were analyzed at the age of 8 months. Experimental groups were compared for disease manifestations including autoantibody production, serum IgG levels, and kidney disease severity.
Results. We found that TLR7 deficiency reduces disease severity and that TLR7 is required not only for the production of autoantibodies against RNA-containing autoantigens but also for autoantibodies against double-stranded DNA. FcgammaIIB-/- mice deficient in both TLR7 and IRF5 developed less disease than mice deficient in TLR7 alone, with lower titers of anti-RNA autoantibodies, lower levels of the pathogenic IgG isotypes, and less severe renal disease.
Conclusions. FcgammaRIIB-/- mice deficient in both TLR7 and IRF5 developed less disease than mice deficient in TLR7 alone, with lower titers of anti-nuclear autoantibodies, lower levels of the pathogenic IgG isotypes IgG2b, IgG2c and IgG3, and less severe renal disease.
We found that although FcgammaRIIB-/- TLR7-/- mice were substantially protected from renal disease as compared to FcgammaRIIB-/- wildtype mice, FcgammaRIIB-/- TLR7-/- IRF5-/- mice were protected to a greater extent. The increased protection may be due to a lower level of glomerular deposition of

the pathogenic isotypes IgG2b, IgG2c and IgG3 in the kidneys of the FcgammaRIIB-/- TLR7-/- IRF5-/- mice. This may reflect the reduced levels of IgG2b, IgG2c and IgG3 in the serum of the FcgammaRIIB-/- TLR7-/- IRF5-/- mice.
In this study we also demonstrate that TLR7 plays a critical role in disease pathogenesis as the severity of most autoimmune manifestations was reduced in TLR7-deficient FcgammaRIIB-/- mice. We found that TLR7 is required for anti-dsDNA autoantibody production in the FcgammaRIIB-/- model. The reduction in anti-Sm/RNP levels was only partial, indicating a TLR7-independent pathway of anti-Sm/RNP production.
In summary, we have demonstrated that TLR7 is a key receptor involved in disease pathogenesis in the FcgammaRIIB-/- mouse lupus model in the absence of the Yaa locus and we have identified TLR7-dependent and TLR7-independent roles for IRF5 in the development of lupus autoimmunity. These findings suggest that therapies targeting IRF5 may offer some additional benefit compared to therapies targeting only TLR7 for the treatment of lupus.

Key words: TLR7, IRF5, autoantibodies

S26:06

INDUCTION OF TYPE-I INTERFERON MRNA IN HUMAN CD14+ CELLS TREATED WITH NEUTROPHIL EXTRACELLULAR TRAPS

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Objective. Neutrophil extracellular traps (NETs) can activate plasmacytoid dendritic cells leading to type-I interferon (IFN) production and contribute to the pathogenesis of systemic lupus erythematosus. NETs can also activate T and B cells. The relation between NETs and monocytes is obscure. The purpose of this study is to assess the role of NETs in the cytokine expression profiles in human peripheral $CD14^+$ cells.
Design and Method. Peripheral blood mononuclear cells (PBMCs) were separated from heparinized blood of healthy volunteer using Ficoll-Paque PLUS® or polymorphprep (TM). $CD14^+$ cells were positively selected using CD14 microbeads. Neutrophils were separated from heparinized blood using polymorphprep (TM). NETs were generated from human neutrophils treated with phorbol-12-mristate-13-acetate (PMA). Purified $CD14^+$ cells were cultured with PMA, lipopolysaccharide (LPS), granulocyte macrophage colony-stimulating factor (GM-CSF) plus interleukin (IL)-4 or NETs. Gene expression levels were quantified using specific primers by real-time PCR or RT-PCR. Expression levels of surface antigen were analyzed by flow cytometer.
Results. Expression levels of type-I IFN (IFN-alpha and beta) mRNA of $CD14^+$ cells treated with NETs were elevated compared to those of $CD14^+$ cells treated with PMA, GM-CSF plus IL-4 or LPS. Expression levels of type-II IFN (IFN-gamma) mRNA of $CD14^+$ cells treated with NETs were decreased compared to those of PBMCs. Expression levels of mRNA of toll like receptors were changed in $CD14^+$ cells treated with NETs. Expression levels of HLA-DR and CD11c were elevated in $CD14^+$ cells treated with NETs compared to $CD14^+$ cells without treatment.
Conclusions. Expression levels of type-I IFN mRNA can be induced in $CD14^+$ cells treated with NETs.

Key words: neutrophil extracellular traps, systemic lupus erythematosus, monocyte

S27: Early lupus and overlap autoimmune diseases

S27:03

SUBCLINICAL RETINAL INVOLVEMENT SYSTEMIC LUPUS ERYTHEMATOSUS AND SJÖGREN SYNDROME PATIENTS

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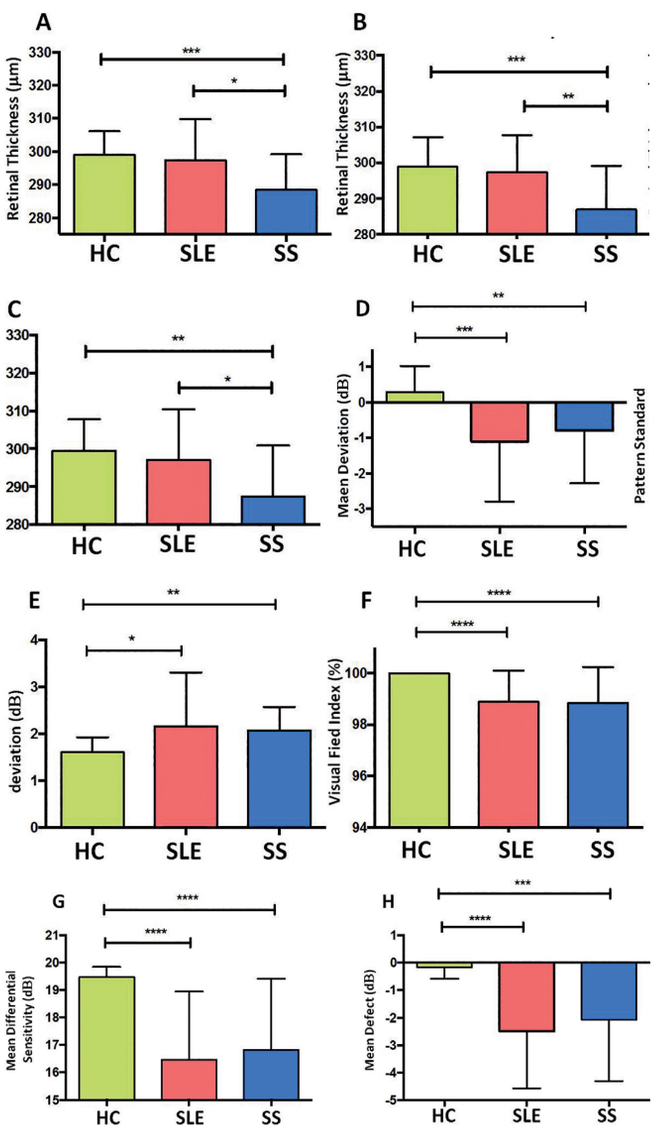
Objective. Eye involvement in Systemic Lupus Erythematosus (SLE) and Sjögren Syndrome (SS) may be not clinically manifest and underestimated. Hydroxycloroquine exert toxic effects on retina. We assessed the subclinical retinal involvement in SLE and SS patients.
Design and Method. 61 patients (36 SLE without secondary SS and 25 primary SS) without clinical eye involvement were enrolled. Morphological and functional eye assessment included: ophthalmological examination, Spectral Domain-Optical Coherence Tomography, standard automated perimetry (SAP), fundus perimetry (FP). 25 healthy controls (HC) were studied.



Results. Retinal thickness in posterior pole in SLE was similar to HC while was reduced in SS than HC and SLE (p=0.0001, p=0.01, Fig.1A). This reduction was demonstrated in superior and inferior hemifield than HC (p=0.006) and SLE (p=0.001, p=0.02) (Fig.1B-C). The thinning in the posterior pole in SS was more

evident in anti-Ro positive patients than in negative ones (p=0.0005). In SLE and SS the mean defect (MD: p=0.008 and p=0.004) and the pattern standard deviation (PSD: p=0.03 and p=0.001) by SAP were increased than HC (Fig.1D-E). Visual field index (VFI) values were reduced in both SLE and SS than HC (p<0.0001, Fig.1F). SLE patients with kidney involvement displayed a significant increase of MD (p=0.04), PSD (p=0.01) and reduced VFI (p=0.04) than those without kidney involvement. In SLE and SS the FP differential sensitivity was reduced (p<0.0001, Fig.1G) and the mean defect values were higher than HC (p<0.0001 and p=0.0002, Fig.1H). A negative correlation was demonstrated in SLE between FP differential sensitivity and age (p=0.04), C3 (p=0.003) and C4 levels (p=0.004). C3 and C4 levels displayed a negative correlation with the cumulative prednisone treatment (p=0.008 and p=0.02). FP alteration in SLE was prevalent in those patients who were not on steroid treatment (p=0.02). In SS a higher proportion of patients with alteration in FP received a cumulative Hydroxycloroquine dose > 1000g (p=0.02).
Conclusions. Subclinical retinal involvement was demonstrated in SLE and SS that might be hidden by treatment. Morphological alterations and functional impairment in SS could be linked to apoptosis of the retinal ganglion cells induced by anti-Ro antibodies or Hydroxycloroquine toxicity. In SLE steroids might exert a protective role. Functional impairment was demonstrated that could be associated to the kidney involvement.

Key words: retina, eye, hydroxycloroquine

S27:04

INTERFERON-RELATED CHEMOKINE CXCL-10(IP-10) IN INCOMPLETE SYSTEMIC LUPUS ERYTHEMATOSUS; A POTENTIAL PREDICTIVE BIOMARKER FOR DISEASE PROGRESSION?

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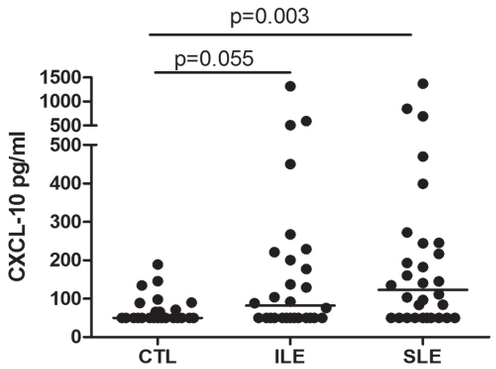
Objective. Incomplete systemic lupus erythematosus (iSLE) is a disease entity describing patients who display symptoms that are typical for systemic lupus erythematosus (SLE), but with insufficient criteria to fulfil the diagnosis. Of these patients, some appear to have a prolonged milder disease course, while others progress to severe SLE. Unfortunately, predictive biomarkers for distinguishing these groups are lacking. Previously, it has been demonstrated that serum levels of CXCL-10 (IP-10), one of the interferon-regulated chemokines, were significantly higher in pre-symptomatic SLE patients compared to healthy controls. Also, in a longitudinal study CXCL-10 (IP-10) levels were found to correlate with lupus activity in SLE patients. Interferon-regulated chemokines therefore could be a possible biomarker for progression to SLE.
Design and Method. We collected serum samples of 28 iSLE patients (defined as positive ANA with titer =/>1:80 and/or anti-SSA and at least one but less than four clinical ACR-criteria), 30 SLE patients (fulfilling ACR criteria and disease duration < 5 years) and 24 healthy controls (HC). In these samples, CXCL-10 serum levels were measured by ELISA (Duoset, R&Dsystems). Clinical data, as well as autoantibody profiles, were obtained.
Results. Both SLE (median 123 pg/ml, range 50-1372) and iSLE (82 pg/ml, range 50-1316) had increased levels of CXCL-10 compared to HC (50 pg/ml, range 50-189). However, this finding was only significant comparing HC vs SLE patients (p=0.0026) and not comparing HC vs iSLE (p=0.055). All HC had CXCL10 levels below 200 pg/ml, while 8 (29%) out of 28 iSLE patients, had levels above 200 pg/ml compared to 10 (30%) of 30 SLE-patients. No correlation was found between levels of CXCL-10 and anti-dsDNA, nor with C3 and C4 in SLE and iSLE patients.



Conclusions. In both iSLE and SLE patients, approximately one third showed increased serum levels of CXCL-10, however only in SLE the level was significantly higher than in HC. It can be hypothesized that those iSLE patients with elevated CXCL-10 levels might progress to SLE. In this case CXCL10 can possibly be used as a predictive biomarker. We will longitudinally follow this group of iSLE patients to confirm this hypothesis.

Key words: CXCL-10/ IP-10, incomplete SLE, biomarker

S27:05

VALUE OF IGA ANTIPHOSPHOLIPID ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND UNEXPLAINED PREGNANCY MORBIDITY

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Objective. Recently, novel SLICC classification criteria for systemic lupus erythematosus (SLE) are proposed. In these new criteria measurements of IgA anti-cardiolipin antibodies (aCL) and IgA anti-β2-glycoprotein I antibodies (anti-β2GPI) are included in addition to the known antiphospholipid antibodies (aPL), since some SLE patients have isolated IgA aPL. In literature this percentage ranges from 0-24%. The question is whether IgA aPL should be measured in all new patients with suspected SLE or only in those with relevant clinical features who test negative for 'classical' criteria aPL assays. Furthermore, we hypothesize that IgA aPL can play a role in the pathogenesis of unexplained pregnancy morbidity.
Aim. To determine the frequency of IgA aCL and IgA anti-β2GPI in a cohort of SLE patients. And to analyse whether these antibodies are more prevalent in women with unexplained pregnancy morbidity. Primary antiphospholipid syndrome (APS) patients are included as reference group.
Design and Method. aPL, including aCL (IgA, IgG, and IgM) and anti-β2GPI (IgA, IgG, and IgM) were measured using EliA (ThermoFisherScientific). Lupus anticoagulans (LAC) was measured by routinely laboratory procedures. One hundred consecutive SLE patients, fulfilling ACR criteria for SLE, and 65 consecutive women with preeclampsia or >2 miscarriages were included. APS patients, fulfilling the Sydney criteria (n=30), were included as reference group.
Results. Six (6%) of the SLE patients had truly positive IgA aPL and six other patients had weakly positive IgA aPL, mostly anti-β2GPI. In 31 of the SLE patients one or more aPL were found, including LAC, aCL and anti-β2GPI. Only one SLE patient, 23 years old, had isolated, but extreme high values of IgA aPL. Interestingly, she suffered from a cerebral vascular event, which was not explained otherwise. In women with unexplained pregnancy morbidity, 2 (3%) had positive IgA aPL, both anti-β2GPI, but in combination with other aPL. In 30% of known APS patients IgA aPL were detected, especially anti-β2GPI.
Conclusions. Routine measurement of IgA aPL is not recommended in SLE. However, when other aPL are negative and APS is still suspected, IgA aPL should be determined. Furthermore, in unexplained pregnancy morbidity measurement of IgA aPL has no additional value.

Key words: SLE, IgA antiphospholipidantibodies, pregnancy morbidity

S27:06

SEROLOGICAL EVOLUTION IN FERTILE WOMEN WITH POSITIVE ANTIPHOSPHOLIPID ANTIBODIES

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Objective. Antiphospholipid syndrome (APS) is characterized by the presence of aPL and at least a clinical event defined as recurrent venous thrombosis, arterial thombosis or pregnancy morbidity. The titers of aPL usually fluctuate, they frequently decrease and eventually become negative during follow-up, thus reducing the risk of thrombotic events.
The aim of this study was to explore the clinical and serological course of fertile women with positive aPL, as well as the factors and the potential therapeutic implications associated with aPL negativization.
Design and Method. We conducted a retrospective study including women attending the obstetric autoimmune pathology clinic. We included 105 women with a confirmed positive APL serology according to Sydney Criteria Patients were classified into 3 different groups: A) patients with primary APS (49), B) patients with a positive serology for APL, not meeting clinical criteria (42) and C) patients with systemic lupus erythematosus and a positive serology for APS (14). They were also classified, according to the serological APL evolution: patients with persistently negative aPL, transiently positive and persistently positive serology according to previously established criteria.
Results. After a mean follow up of 114,4 ± 37,2 months, 59% patients had persistently negative antibodies, while 25,7% patients presented persistently positive aPL serology. After the multivariate analysis only the tobacco use (OR 3,5 p=0,013) was confirmed as an independent risk factor. The load of antibodies, specially the presence of triple positivity (OR: 2,4; IC: 0,16-2,36), was close to statistical significance (p=0,162). No other factors, including traditional cardiovascular risk factors, treatments or clinical manifestations reached statistical significance. Persistent positivity was associated with higher risk for further pregnancy morbidity (41 vs 52 %; p=0,328). In 17 patients, with persistently negative serology who were asymptomatic, treatment with low dose aspirin was discontinued. No clinical events related to APS were reported after treatment withdrawal, during a 119,9 months follow-up period.
Conclusions. Our study suggests that among fertile women, aPL remain persistently positive only in one quarter of patients, being tobacco use an independent risk factors for its persistence. Among patients with persistently negative serology and with a low-risk profile discontinuation of antiplatelet therapy could be considered a safe choice.

Key words: antiphospholipid antibodies, serological evolution, risk factors

S28: Biomarkers and risk stratification in lupus

S28:03

SLE-KEY® ICHIP® PLATFORM IDENTIFIES A 'LUPUS AUTOANTIBODIES SIGNATURE' EARLY IN DISEASE WHICH PERSISTS INDEPENDENT OF DISEASE DURATION AND ACTIVITY

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Objective. We previously described the development of an iCHIP® microarray technology platform (1) to rule out the presence of systemic lupus erythematosus (SLE). Here we report an SLE-key® linear discriminant analysis (LDA) classifier (2) that detects an SLE autoantibody signature, which persists independent of the time after diagnosis and the level of disease activity.
Design and Method. We analyzed autoantibody patterns in serum samples of 246 SLE patients and 252 self-declared healthy controls; the array contained 200 antigens and detected profiles of IgG and IgM antibodies. SLE disease activity indexes (SLEDAI) were available for 232 patients and ranged from 0 to 25. SLE samples were collected from patients less than 1 year after diagnosis, 1, 2 and 3 years after diagnosis (median 1.00±1.00) with 41, 102, 55, 47 patients per group, correspondingly.
Results. The iCHIP® autoantibody profile analyzed with the LDA algorithm identified a robust and consistent lupus-specific signature based on autoantibodies binding to a combination of nucleic acid (complex ssDNA and a defined oligonucleotide) and protein biomarkers that discriminates between lupus and unaffected subjects with 94% sensitivity, 75% specificity and 93% NPV. The lupus signature is independent of time after diagnosis with a median LDA score of 0.93±0.26, 0.84±0.33, 0.9±0.3 and 0.87±0.32 for <1, 1, 2, and 3 years after diagnosis, respectively. The different time after diagnosis patient groups were compared and no features were found to significantly distinguish between the groups (p>0.05 for all features, corrected for multiple hypothesis). This lupus signature is present in patients irrespective of disease activity. Patients with active disease (SLEDAI >3) had a median LDA score of 0.95±0.25. Inactive (SLEDAI =0) patients had a median LDA score of 0.8±0.33 and are thus easily differentiated from healthy individuals with median LDA score of 0.10±0.14. In addition, 100 features demonstrated significant differences (p<0.05) between inactive SLE patients and healthy controls. An AUC of 0.89 was obtained based on the median performance of multiple support vector machine (SVM) classifiers applied in a cross-validation work-frame.
Conclusions. The SLE-key® microarray test that we previously reported for reliably ruling out SLE (2) detects a lupus signature close to diagnosis which persists independent of disease activity or duration. This signature is stable, and even patients with inactive disease are clearly differentiated from healthy individuals. In development are other unique signatures to monitor disease activity and to correctly identify early SLE in patients that do not (yet) fully meet ACR and/or SLICC criteria.

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Key words: systemic lupus erythematosus, autoantibodies, iCHIP

S28:04

DISCOVERY AND INITIAL VALIDATION OF AUTOANTIBODIES AGAINST THE MAJOR VAULT PROTEIN (MVP) IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. In systemic lupus erythematosus (SLE), early diagnosis and prognostic stratification are still great challenges. The broad characterization of the autoantibody repertoire in SLE is an emerging tool to supporting a personalized disease management approach. We have recently conducted autoantibody profiling studies of SLE, systemic autoimmune diseases (AID), and healthy controls to identify biomarkers for improving lupus diagnosis and patient stratification. Here we describe the identification of autoantibodies against the major vault protein (MVP) in SLE.
Design and Method. A large-scale Luminex bead-based autoantibody screen was conducted by combining diagnostic with putative antigens. In the discovery phase the autoantibody reactivity of serum samples from 130 SLE patients, 794 AID patients (systemic sclerosis, rheumatoid arthritis/RA, early RA) and 343 healthy controls was tested against 6,912 recombinant human proteins. Following validation in independent SLE samples (n=101), consistent autoantibody reactivity against 46 antigens was found (*p*-value <0.05 and Cohen's d effect size <0.3).
Results. A data base search of 46 known and novel SLE-associated antigens revealed that the expression of ten proteins is upregulated by type I interferon (INF) (http://www.interferome.org). Beyond known antigens (TRIM21/Ro52, SSB), we identified a novel autoantibody target MVP with a frequency of 20% in SLE. Anti-MVP antibodies are also found in SLE patients tested negative for dsDNA, Sm, and ribosomal P. Interestingly, MVP is the major constituent of the vault particle, which is a cytoplasmic organelle and the largest known ribonuclear protein complex. Although the exact biological function of MVP is not well understood, literature data suggest that MVP is a virus-induced host factor, which up-regulates type I INF production.
Conclusions. Anti-MVP autoantibodies represent a useful marker in SLE and - in combination with anti-dsDNA, anti-Sm and anti-ribosomal P - optimizes the strategy for SLE autoantibody testing. Although more studies are needed, our findings suggest a previously undescribed linkage of type I INF and autoantibody targets in SLE.

Key words: autoantibody, SLE, diagnostics

S28:05

INCREASED SERUM LEVELS OF IFN-LAMBDA 1 CORRELATE WITH TH17 AXIS CYTOKINES AND INDEPENDENTLY TO IFN-ALPHA IDENTIFY PATIENT GROUP WITH HIGHER ORGAN DAMAGE

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Objective. Type I interferons (IFN), particularly IFN- αs, are considered to have a pivotal role in SLE. Recently, increased levels of type III IFNs (IFN-λs have been described to be also associated with SLE.
In this study, we measured circulating levels of IFN-λ1, IL-17, IL-23 and also IFN-α in a cohort of SLE patients and investigated their association with clinical and laboratory manifestations of the disease. Population controls were investigated as comparators.
Design and Method. 261 SLE patients and 276 population controls, identified through the population registry and matched for age, sex, and region of living, were included. All participants were examined by clinician rheumatologist and assessed for current organ manifestations and disease related organ damage. Sera were collected at inclusion and stored at -70* C until analysis. Serum levels of IFN-α, IFN-λ1, IL-17 and IL-23 were measured in sera by commercial ELISA.
Results. IFN- λ1 was detected in 76 (29,1%) patients and IFN-α in 115 (44%). In 108 patients (41.4%) neither of the cytokines was detected. Both IFN-λ1 and IFN-α were detected more often and in higher levels in patients. IFN-lλ1 levels did not correlate to the levels of IFN-α, and only in 38 (14.5%) patients had detectable levels of both. Levels of IL-17 and IL-23 correlated with each other and with IFN-lambda 1. In comparison, only a weak correlation between levels of IFN-alpha and IL-23 was observed. Significantly increased levels of IFN- λ1 were associated with lower incidence of fever, photosensitivity and also arthritis. Patients with high IFN-α more often had active mucocutaneous disease, lymphadenopathy, lower levels of C3 and C4, and also presence of anti-Ro/SSA and anti-La/SSB. The incidence of thromboembolic events and overall vascular events was lower in this group, as well as lower frequency of antiphospholipid antibodies (LAC, aCL and B2GP1 IgG). Co-upregulation of IFN-α and IFN-lλ1 was significantly associated with overall higher disease activity (SLAM), and such manifestations as lymphadenopathy and cortical dysfunction, seizures and anti-Ro52 and Ro60/SSA abs.
IFN-α was associated with overall lower disease damage. However, IFN-λ1 was associated with lower incidence of musculoskeletal damage. The triple detection of IFN- λ1, IL-17 and IL-23 was significantly associated with overall higher disease damage score, and particularly higher incidence of renal impairment (GFR<61, MDRD).
Conclusions. Our study demonstrates that in SLE patients the levels of IFN-α and IFN-λ1 do not correlate, but rather dissect patients with different target organs, however increased levels of both cytokines are associated with overall higher disease activity. Increased levels of both IFN- λ1, IL-17 and IL-23 are associated with the higher disease damage, and particularly kidney damage.

Key words: interferon,Th-17, disease activity

S28:06

ANGIOGENESIS BIOMARKERS AND DOPPLER ULTRASOUND IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND/OR ANTIPHOSPHOLIPID SYNDROME FOR DIFFERENTIAL DIAGNOSIS BETWEEN PREECLAMPSIA AND DISEASE ACTIVITY

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Objective. Preeclampsia (PE) affects 2-5% of healthy women. This risk increases up to 10-30% in autoimmune diseases. Differential diagnosis between PE and flare during pregnancy is often difficult. Pulsatility index of uterine arteries (mPI-UtA), serum levels of endoglin and the ratio tyrosine kinase-like soluble receptor/ placental growth factor (sFlt-1 / PlGF) are useful for early diagnosis, even in asymptomatic women. Our aim was to analyse the utility of these markers among pregnant patients with Systemic Lupus Erythematosus (SLE) and/or Antiphospholipid Syndrome (APS).

Mean (± SD)		Normal Pregnancy	Flare	PE
24 weeks	UtAmPI	0.91 (±0.27)	0.76 (±0.11)	1.4 *(only performed in 1 patient)
	Ratio (<14.8)	9.27 (±19.15)	6.83 (±3.82)	12 (±7.10)
	sEndog (<7.9)	6.91 (±4.83)	6.02 (±2.78)	14.7 (±0.16)
28 weeks	UtAmPI	0.71 (±0.16)	0.69 (±0.23)	1.1*
	Ratio (<16.9)	5.04 (±5.75)	8.15 (±9.23)	19.8 (±23.76)
	sEndog (<7.2)	9.89 (±5.54)	8.96 (±6.31)	16.9 (±14.25)
32 weeks	UtAmPI	0.69 (±0.11)	0.65 (±0.13)	0.9*
	Ratio (<86.4)	4.77 (±7.45)	19.17 (±15.13)	89.6 (±114.70)
	sEndog (<13.6)	10.51 (±4.18)	9.58 (±4.70)	35.6 (±19.44)

Design and Method. We included patients followed in our high-risk pregnancy clinic from 2008 to the present with diagnosis of SLE, LES-like, APS or antiphospholipid antibodies without fulfilling criteria APS (aPL). PE were diagnosed according to the International Society for the Study of Hypertension in Pregnancy criteria (ISSHP). Lupus activity was assessed with moderate considering SLEPDAI index >6 and APS according to clinical activity. Follow-up visits were performed at 11-13, 22, 28 and 32 weeks and postpartum. We collected clinical data about autoimmune disease and pregnancy, analytical data, endoglin, ratio and mPI-UtA. We performed a descriptive analysis, Chi-square or t-Student tests according to the type of variable. Odds ratio and confidence intervals were calculated by using simple logistic regression.
Results. We analysed 58 pregnancies. Lupus activity was detected in 6 patients (10.3%). Two patients developed moderate to severe activity (SLEPDAI 25 and 12, respectively) with worsening since 24th week (33.3%). Two patients with SLE ± APS developed PE (3.4%). We found statistically significant association between PlGF and ratio in 32 week and development of PE [(mean 151.76±118.85 with p=0.023) and (89.62±114.70 with p=0.020), respectively)]. In addition, endoglin, ratio and mPI-UtA were higher in PE than in normal pregnancy or flares since 24 week. On the other hand, there not seems to be differences in scores between patients with lupus activity and normal pregnancy (see table).
Conclusions. Despite the limited number of patients, it seems that the mPI-UtA, endoglin and ratio in patients with SLE and / or APS behaves as in the general population and may help in the differential diagnosis of preeclampsia and disease activity.

Key words: pregnancy, SLE, biomarkers

S29: Improving outcome in SLE

S29:03

EVALUATION OF SELF REPORTED FATIGUE IN ADULT ITALIAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: ASSOCIATION WITH GENERAL HEALTH, QUALITY OF LIFE AND MUSCULOSKELETAL MANIFESTATIONS

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Objective. Fatigue represents one of the most frequent manifestations in Systemic Lupus Erythematosus (SLE) patients, reported by 80% of cases, influencing the quality of life. The assessment of fatigue could be difficult. The Functional Assessment of Chronic Illness version 4 Therapy (FACIT-F) questionnaire has been validated in chronic diseases to assess fatigue in adult patients with chronic diseases. We aimed at assessing the fatigue, by using FACIT-F questionnaire, in a monocentric cohort of SLE patients. Moreover, we evaluated possible associations with others clinical manifestations, laboratory parameters, activity and chronicity indices and general health index (GH).
Design and Method. We enrolled consecutive SLE patients, fulfilled the 1997 American College of Rheumatology (ACR) revised criteria during 1-month follow-up. Clinical and laboratory data were collected in a standardized, computerized and electronically filled form, including demographics, past medical history with date of diagnosis, comorbidities, and previous and concomitant treatments. We assessed the disease activity and chronic damage by using SLEDAI-2K and SDI, respectively. The GH (range 0-100) was assessed. Finally, all the patients completed the FACIT-F, a 13-item questionnaire assessing self-reported tiredness, weakness, and difficulty in usual activities due to fatigue. A five-point intensity type of rating scale (from "not at all" to "very much") is used. Final scores are the sum of responses and range from 0 to 52; higher scores indicated less fatigue.
Results. One hundred forty-seven SLE patients (13M/134F; mean age 40.4±11.7 years; mean disease duration 123.7±90.8 months) were evaluated. We obtained a mean SLEDAI-2K of 1.8±2.8 and a mean SDI of 0.3±0.7. Fibromyalgia (34.5%) and comorbid depressive and anxiety spectrum disorders (27.6%) were the major comorbidity founded. A significant correlation between the FACIT-F values and GH was identified (63.0±19.2; r=0.67, p<0.0001). Conversely inverse correlation was identified between the FACIT-F values and patient's ages (r=-0.256; p=0.001). SLE patients with joint involvement showed a significantly lower mean FACIT-F value than patients without (31.5±10.7 versus 36.2±11.4; p=0.004). Moreover, SF-36 questionnaire was administered in 38 patients. A significant correlation between the FACIT-F score and all the values obtained from the 8 sections of the SF-36 was registered [general health perceptions (r=0.7; p<0,0001); mental health (r=0.6; p<0,0001); physical functioning (r=0,6; p<0,0001); emotional role functioning (r=0.3; p=0,03); emotional role functioning (r=0.4; p=0,0031); bodily pain (r=0.6; p<0,0001); social role functioning (r=0.7; p<0,0001); vitality (r=0.8; p<0,0001)]. No significant association has been identified between FACIT-F values and the presence of fibromyalgia and comorbid depressive and anxiety spectrum disorders.
Conclusions. In the present study, conducted on a large SLE cohort, fatigue was significantly associated with health status and quality of life. Moreover, musculoskeletal involvement represents the only disease manifestation significantly correlated with the presence of fatigue.

Key words: systemic lupus erythematous, fatigue, quality of life

S29:04

SLE PATIENTS' CONCERNS AND ADHERENCE TO THERAPY – A QUALITATIVE STUDY

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Objective. We believe that the concerns and expectations of patients with Systemic Lupus Erythematosus (SLE) influence their adherence to treatments and also their compliance with medical visits and diagnostic tests proposed. Our objectives are: 1) to identify the main concerns and expectations of patients with SLE regarding their disease and treatments; 2) to assess the relation between these concerns and the adherence to treatments.

Design and Method. We performed a qualitative study using a convenient sample of SLE patients attending an outpatient rheumatology clinic. Inclusion criteria included age >18 years old; disease duration >1 year and fulfilment of ACR (1997) or SLICC classification criteria. Patients with cognitive impairment were excluded. All participants gave informed signed consent and the study was approved by the local ethics committee. Semi-structured interviews were conducted and audiotaped. The full transcripts were integrated into a MAXQDA project file. The data was analysed by two different coders using content analysis methodology. A code book was discussed and implemented. The intercode agreement was evaluated during the data analysis process.
Results. Fifteen participants were included (14 female and 1 male), with a median age of 40 (IQR: 36-45,5) years old and a median disease duration of 11 (IQR: 6,5-15) years.
Emergent themes regarding patients' concerns included fear of disease worsening and becoming dependent; capacity to take care of their children and the possibility of transmitting SLE to the outspring. Participants reported, as main implications of their disease, pain and fatigue that interfere with domestic and professional activities, and also with their social and sexual lives; having to avoid outdoor leisure activities, namely going to the beach; and aesthetic issues. These patients feel more confident knowing they have periodic both clinical and laboratory evaluation. Main reasons for adherence to therapy are trust in medication to avoid manifestations of SLE; routine; trust in the rheumatologist and feelings of obligation. Non-adherence is more common in the beginning of the treatment because of difficulty in accepting a chronic disease which requires lifelong therapy. Other reasons for non-adherence include oblivion, neglect and adverse effects of the medication.
Conclusions. Our research data underlines the important interplay between adherence to medication and the possibility to gather accurate information and proper support during the treatment process. The latter is particularly relevant considering the reported psychological effects of a chronic disease requiring lifelong therapy. Collected evidence suggests that efficient patient education strategies may be important to improve adherence to therapy in SLE.

Key words: patient's perspective, adherence to therapy, qualitative study

S29:05

SOCIAL SUPPORT AND QUALITY OF LIFE IN SLE

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Objective. In the last decades, the relationship between social support (SS) and health in systemic lupus erythematosus (SLE) patients has received a growing attention. Some studies demonstrated that SS can impact on disease activity, damage and quality of life (QOL), although the precise ways in which SS contributes to health are not completely understood. This contribution presents the results of three studies with the aim of moving a step ahead in the comprehension of SS from patients' perspective. A specific attention is devoted to "problematic SS" (*i.e.*, instances of support that are perceived as non-supportive by patients).
Design and Method. Three studies are presented. Study 1: we explored the experiences of positive and problematic SS as perceived by patients. Nine women with SLE were interviewed and transcripts were analyzed through qualitative content analysis. Study 2: a survey was conducted with a sample of 344 Italian patients, to investigate the relationship between positive and problematic SS, stress and QOL. Study 3: we investigated the effect of problematic SS and self-efficacy on QOL through a longitudinal design with 162 patients.
Results. Study 1: different types of problematic SS emerged, like "oppressive support" (characterized by excessive worries and unwanted advices) and "denying support" (that neglects the disease and its consequences). Study 2: results showed that the relationship between SS (positive and problematic) and quality of life was mediated by the experience of stress. Study 3: controlling for corticosteroids and hydroxychloroquine use, self-efficacy in the management of the disease at Time 1 showed a significant and positive effect on health-related QOL at Time 2, while problematic SS (denying/uninformed) showed a negative effect.
Conclusions. The role of problematic SS confirmed its relevance for the life of SLE patients. In a such complex disease, that involves periods of relative suffering, alternating with periods of relative comfort, family members, friends, doctors and health professionals, must learn when to give and when to withhold help, as providing too much support or providing it at the wrong time could even produce negative outcomes. Detailed implications of findings for professionals and for patients are discussed.

Key words: social support, quality of life, patients perspective

S29:06

DETERMINANTS OF QUALITY OF LIFE IN SYSTEMIC LUPUS ERYTHEMATOSUS: A SINGLE CENTER EXPERIENCE

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Objective. Despite significant advances in the pathobiology and management of systemic lupus erythematosus (SLE), quality of life (QoL) is commonly impaired, reflecting the burden of disease.
The aim of our study was to assess QoL in lupus and to determine potential predictors of disability in different SLE settings.
Design and Method. Prospective observational study in 120 consecutive SLE patients (fulfilling either 1987 ACR or new 2012 SLICC/ACR diagnostic and classification criteria) with a mean age of 36.9+/-15.2 years and a mean disease duration of 9.2+/-8.5 years attending the outpatient rheumatology department.
Demographic, clinical, immunologic profile, disease activity (SLEDAI), organ damage (SLICC/ACR) as well as QoL (Short Form-36, HAQ-DI) were collected in all patients at least once.
Health assessment survey was focused not only on separate domains such as Physical Function (PF), Role Physical (RP), Role Emotional (RE), Social Function (SF), Bodily Pain (BP), Mental Health (MH) and Vitality (VT), but was also evaluated as two key components meaning physical (PCS)- and mental (MCS).
Univariate and multivariate analysis was done in SPSS, $p<0.05$.
Results. Statistical significant negative correlation between different SF-36 domains and disease activity and organ damage was reported: lower PF, RP, RE, SF, VT, higher SLEDAI ($p<0.05$) and higher SLICC/ACR ($p<0.05$); moreover, lower PCS component was also associated with higher SLE damage, while MCS correlated with new flare and SLE activity.
Furthermore, when adjusting for disease duration, we demonstrated that lower SF, PF, PCS ($p<0.05$) but no correlation with RE and MCS ($p>0.05$) were identified in SLE with long history of SLE; however, a recent onset of the disease was typically associated with impaired RE and MCS ($p<0.05$.
No specific influence of immune abnormalities on SF-36 parameters was defined in our patients.
Conclusions. Disease activity and organ damage as well as SLE flare and new organ involvement were significantly associated impaired QoL, being independent predictors of disability.
Physical dimension of health survey was typically associated with disease duration and damage, while the mental one correlates better with newly diagnosed SLE, flare and new-organ involvement.

Key words: systemic lupus erythematosus, quality of life, SF36

S30: Lupus animal models and new pathogenetic clues

S30:04

MICROPARTICLES BIND TO CIRCULATING PHAGOCYTES AND ERYTHROCYTES: A POSSIBLE CLEARANCE MECHANISM RELEVANT TO THE PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective. Circulating microparticles are hypothesized to play an important role in the pathogenesis of systemic lupus erythematosus (SLE). Impaired clearing of microparticles may lead to activation of the immune system, autoantibody production, and tissue deposition of immune complexes as well as antibody-covered microparticles. However, the exact mechanisms remain unclear. We examined surface characteristics of microparticles and their capacity to bind to circulating phagocytes and erythrocytes from SLE patients and healthy individuals.
Design and Method. Surface characteristics of microparticles from 18 SLE patients and 11 healthy individuals were assessed by flow cytometry using leukocyte subtype surface markers and antibodies against complement fragments: anti-C3d (recognizing all bound C3 fragments), anti-C3b/iC3b and anti-iC3b, respectively. Flow cytometry was also used to assess the ability of microparticles labelled with 5-(and-6)-carboxyfluorescein diacetate succinimidyl ester to bind to autologous phagocytes and erythrocytes after 1, 5, 15, 30 and 60 minutes of incubation in the presence of autologous serum.
Results. Microparticles from SLE patients had a higher total amount of bound C3 (p=0.026) but fewer opsonising C3b/iC3b molecules (p=0.004) on their surface than microparticles from healthy individuals. The C3b/iC3b-level correlated with that of plasma C3 (rs=0.53, p=0.036). Granulocytes and monocytes from SLE patients as well as from healthy individuals rapidly bound autologous microparticles, with maximal binding being reached within the first 15 minutes of incubation. Granulocytes from SLE patients bound more microparticles than granulocytes from healthy individuals (p=0.046). Moreover, microparticles bound to erythrocytes, and this binding increased progressively over the entire observation period. The presence of erythrocytes inhibited the binding of microparticles to granulocytes by approximately 50%.
Conclusions. The reduced carriage of opsonizing C3 fragments, despite the increased total number of C3 fragments, on microparticles from SLE patients supports the hypothesis of defective clearance of apoptotic material in SLE. We found that erythrocytes bound microparticles competitively and thereby acted as a buffer for circulating microparticles. This finding, combined with the fact that SLE erythrocytes express low copy numbers of CR1, point to an important mechanism of clearance deficiency in patients with SLE. Given the emerging role of granulocytes as important effector cells in SLE, our finding of increased binding of microparticles to SLE granulocytes is likely to be of pathological relevance.

Key words: microparticles, clearance, complement

S30:05

ROLE OF GALECTIN-3 IN PREVENTION AND TREATMENT OF LUPUS GLOMERULONEPHRITIS IN NZB/NZW F1 MICE

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Objective. Lupus glomerulonephritis (LGN) is a severe autoantibody-mediated manifestation. Galectin-3 (gal-3) can potentially reduce autoantigen availability contributing to B cell tolerance. Our aim was to explore the effects of gal-3 administration on LGN.
Design and Method. 40 female NZB/NZW F1 mice were split into 4 groups of 10 mice each and intraperitoneally injected once a week with gal-3 100µg in 100µl of PBS (gal-3-treated mice) or PBS 100µl (controls) starting at 12 weeks of age (preventive approach) or after the onset of proteinuria levels greater-than or equal to 30mg/dl (therapeutic approach). Every 4-6 weeks we collected blood samples to evaluate serum levels of gal-3, BLyS (B lymphocytes stimulator factor), anti-double-stranded(ds)DNA and anti-C1q antibodies by ELISA tests. Proteinuria levels were assessed weekly by multistix reagent strips. At death, organs were harvested for histological analyses. Survival and proteinuria-free survival were evaluated by Kaplan-Meier method using SPSS 22 software.

Table I. Circulating autoantibodies levels, Gal-3, BLyS, and proteinuria levels in Group 1 (preventive Gal-3 treatment) Group 2 (preventive PBS controls), Group 3 (therapeutic Gal-3 treatment), Group 4 (therapeutic PBS controls) mice, expressed as the median (min-max) of the mean OD of the double of every serum for antibodies, median (min-max) of the mean concentration (pg/ml) for Gal-3 and BLyS or (mg/dl) for proteinuria.

	Group 1	Group 2	Group 3	Group 4
Anti-Clq				
W12	0.320 (0.120-0.476)	0.458 (0.264-0.718)	0.227 (0.149-0.978)	0.43626 (0-0.954)
W16	0.396 (0.215-0.658)	0.712 (0.515-0.936)	0.415 (0.334-0.712)	0.53480-(0350-0.785)
W21	0.451 (0.333-0.623)	0.852 (0.735-0.970)	0.561 (0.420-0.803)	0.797 (0.390-1.014)
W26	0.763 (0.349-0.862)	1.541 (1.382-1.773)	1.451 (0.954-1.861)	1.539 (0.679-2.178)
W32	1.786 (0.740-2.125)	1.996 (1.603-2.681)	1.441 (0.709-2.526)	
W38	0.696 (0.443-1.396)		0.881 (0.573-1.396)	
W42	0.928 (0.928-0.928)		0.828 (0.576-1.276)	
Anti-dsDNA				
W12	0.076 (0.035-0.216)	0.101 (0.060-0.215)	0.107 (0.076-0.206)	0.096 (0.034-0.258)
W16	0.105 (0.049-0.350)	0.168 (0.065-0.286)	0.139 (0.053-0.285)	0.315 (0.133-0.803)
W21	0.119 (0.024-0.384)	0.539 (0.036-0.971)	0.141 (0.081-1.004)	0.477 (0.075-1.994)
W26	0.549 (0.246-0.940)	1.095 (0.801-1.880)	1.160 (0.749-1.626)	1.357 (0.693-1.928)
W32	1.447 (0.752-2.676)	1.717 (1.212-2.838)	1.867 (1.498-3.149)	
W38	2.037 (1.515-2.499)		2.044 (0.598-2.838)	
W42	3.173 (3.173-3.173)		2.358 (0.111-2.876)	
Gal-3				
W12	83.08 (52.67-202.67)	219.75 (61.00-830.17)	90.15 (6.82-191.26)	52.92 (13.50-84.33)
W16	280.06 (94.59-799.78)	158.43 (119.14-596.64)	225.91 (92.71-412.71)	171.65 (72.7-560.2)
W21	286.11 (107.71-706.64)	291.04 (45.04-1184.24)	475.17 (205.2-890.2)	190.04 (17.4-1265.6)
W26	744.20 (114.20-1643.95)	217.09 (31.81-1120.70)	882.04 (226.04-1333.8)	355.3 (40.15-627.2)
W32	1301.74 (129.24-1472.24)	253.95 (83.37-1000.78)	1214.95 (1112.95-1375.2)	
W38	1285 (1179.95-1619.95)		1567.45 (1300.7-1923.95)	
W42	1464.45 (1464.45-1464.45)		1186.58 (1105.45-1471.20)	
BLyS				
W12	600 (430.71-1133.57)	555 (435-1110)	613.9 (424.3-1395)	643.9 (402.86-801.4)
W16	748.75 (432.5-1662.5)	751.25 (550-1167.5)	672.5 (435-872.5)	772.5 (532.5-1435)
W21	2375.36 (1894.3-3525)	1007.14 (552.9-2650.7)	2239.3 (722.1-2590.7)	1671.4 (531.4-2535)
W26	737.14 (355.7-1238.6)	895.7 (390-2950.7)	607.5 (336.4-1965)	1969.3 (833.6-2110.7)
W32	677.14 (578.6-1958.6)	2875.7 (715.7-4176.4)	1774.29 (317.14-5370.0)	
W38	1433.57 (1000.0-5314.29)		726.43 (535.71-1517.14)	
W42	9503.57 (9503.57)-9503.57)		3021.43 (452.14-8629.29)	
Proteinuria				
W16	0 (0-0)	0 (0-30)	15 (15-30)	0 (0-15)
W20	0 (0-0)	22.5 (0-100)	15 (0-30)	30 (15-2000)
W22	15 (0-100)	65 (15-2000)	15 (15-100)	30 (15-100)
W25	15 (0-100)	65 (0-100)	30 (15-2000)	300 (30-2000)
W27	100 (30-300)	100 (100-300)	100 (30-300)	2000 (2000-2000)
W31	100 (15-2000)	100 (100-300)	100 (15-2000)	2000 (2000-2000)
W32	2000 (100-2000)	1150 (300-2000)		

Footnotes: anti-Clq: antibodies against complement Clq components; anti-dsDNA: antibodies against double stranded DNA; Gal-3: galectin-3; BLyS: B lymphocytes stimulator factor:

Results. Data are reported in Table I. In the preventive approach, anti-dsDNA and anti-C1q antibodies appeared at lower levels in gal-3-treated mice compared with controls (anti-dsDNA: week 21, p=0.004; week 26, p<0.0001; anti-C1q: week 16, p<0.0001; week 21, p<0.0001; week 26, p<0.0001). Proteinuria levels were also reduced in gal-3-treated mice (preventive approach: week 20, p=0.002; week 22, p=0.023; therapeutic approach: week 27, p<0.0001; week 31, p=0.024). Gal-3 circulating levels were increased in gal-3-treated mice; no difference in BLyS serum levels was observed between treated and control mice.
In both preventive and therapeutic approaches, gal-3-treated mice showed significantly higher proteinuria free survival (p=0.027 and p<0.0001, respectively) and lived significantly longer than controls (p=0.010 and p<0.0001, respectively). In this model, systemic administration of gal-3 did not enhance kidney and hearth fibrosis.
Conclusions. Preventive and therapeutic administration of gal-3 delays LGN and prolongs survival of NZB/NZW F1 mice.

Key words: Galectin-3, lupus glomerulonephritis, NZB/NZW F1 mice