01 – THIRD SESSION: Osteoarthritis and its management

S3:1

OSTEOARTHRITIS AND ITS MANAGEMENT - EPIDEMIOLOGY, NUTRITIONAL ASPECTS AND ENVIRONMENTAL FACTORS

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OA: epidemiology. Osteoarthritis (OA) is the most prevalent chronic rheumatic diseases worldwide, with a strong impact on function, overall quality of life (QoL), including mental health, healthcare resource utilisation and potential impact on cardiovascular morbidity.
OA is a clinically heterogeneous disease presenting with different clinical phenotypes recognising different systemic and local risk factors. Among them, some factors are not modifiable, including sex and genetic background, and - in some extent - joint alignment and deformity, bone density, and concurrent joint disorders (e.g. rheumatoid arthritis, crystal deposition arthritis, trauma and surgery). However, even in these cases, risk stratification and early diagnosis might play a role in improving long-term outcomes, at least interfering with other modifiable risk factors, following primary or secondary prevention strategies.
OA: Nutritional aspects. Obesity is one of the most important modifiable risk factor for OA - mainly for the Knee OA (KOA) -, with consistent evidence of symptomatic and structural benefit of weight loss.
The Osteoarthritis Initiative study program has strongly contributed to elucidate the potential role of selected diet-related factors in modulating the risk of development or progression of OA.
High dietary fiber intake associates with lower pain scales in KOA and lower probability of symptomatic KOA. Other evidence supports the role of soy milk in lowering worse structural outcomes. Interestingly, higher adherence to the Mediterranean diet, measured with Mediterranean diet score, was independently associated with lower prevalence of OA and better QoL, function and depressive symptoms. This association seems to be related to the intake of cereals. A randomised controlled trial (RCT) enrolling KOA patients found a significant short-term effect of the Mediterranean diet on serum biomarkers of cartilage degradation, such as cartilage oligomeric matrix protein (sCOMP).
Moreover, in a RCT on Vitamin D supplementation in patients with KOA, the active arm achieving sufficient levels of 25-hydroxicolecalciferol showed lower inflammatory features, better function and lower cartilage damage than controls.
OA: Environmental factors. Other potential environmental risk factors of OA include demanding physical activities or occupations requiring repeated motions. Physical activity certainly carries a potential protective effect, mediated by weight control and maintenance of muscle strength (mainly at the quadriceps muscles). However, sports might also act as risk factor, but their association is controversial and it seems to be mediated by injuries occurring during participation rather than physical activity itself.
Conclusion. OA optimal management remains one of the biggest unmet medical needs in rheumatology, with no major disease modifying OA drugs available at present. Interfering with nutritional and environmental modifiable risk factors is a viable and safe strategy that might help in preventing and limiting the consequences of the disease.

S3:2

OSTEOARTHRITIS AND ITS MANAGEMENT: NEW ASPECTS ON THE ROLE OF IMAGING

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Background. The increased availability of modern imaging in clinical practice has led to its more extensive use. Particularly, this is applicable in osteoarthritis (OA), that represents the most common arthropathy, and a major cause of pain and disability worldwide. Thus, a need for defining the role of imaging in the management of this disease in clinical practice has emerged (1).
Methods. Recently, with the aim of developing evidence-based recommendations for the use of imaging in the clinical management of OA, a task force convened by the European League Against Rheumatism (EULAR) and including rheumatologists, radiologists, generalists, methodologists and patients from 9 European countries developed recommendations based on both evidence obtained through systematic literature review (SLR) and expert opinion (1).
After identifying the areas of application of imaging in OA, research questions were developed to drive the SLR. In terms of imaging techniques, conventional radiography, ultrasound, magnetic resonance imaging, computed tomography and radioisotope scan were included in the SLR, with a focus on knee, hip, hand and foot.
Results. Based on the priorities identified by the task force, the role of imaging in making a diagnosis of OA and identifying OA features (including soft tissue, bone and cartilage involvement), in detecting alternative diagnoses, the impact of imaging on disease management, in defining prognosis (natural history of the disease and response to treatment), in the follow up of the disease and to guide treatment were addressed in seven recommendations.

Recommendation	SOR, mean (95% CI)
1) Imaging is not required to make the diagnosis in patients with typical* presentation of OA. *typical features include: usage-related pain, short duration morning stiffness, age>40, symptoms affecting one or a few joints.	8.7 (7.9, 9.4)
2) In atypical presentations imaging is recommended to help confirm the diagnosis of OA and/or make alternative or additional diagnoses.	9.6 (9.1, 10)
3) Routine imaging in OA follow-up is not recommended. However, imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics to determine if this relates to OA severity or an additional diagnosis.	8.8 (7.9, 9.7)
4) If imaging is needed, conventional (plain) radiography should be used before other modalities. To make additional diagnoses, soft tissues are best imaged by US or MRI and bone by CT or MRI.	8.7 (7.9, 9.6)
5) Consideration of radiographic views is important for optimizing detection of OA features, in particular for the knee weightbearing and patellofemoral views are recommended.	9.4 (8.7, 9.9)
6) According to current evidence, imaging features do not predict non-surgical treatment response and imaging cannot be recommended for this purpose.	8.7 (7.5, 9.7)
7) The accuracy of intra-articular injection depends on the joint and on the skills of the practitioner and imaging may improve accuracy. Imaging is particularly recommended for joints that are difficult to access due to factors including site (e.g. hip), degree of deformity and obesity.	9.4 (8.9, 9.9)

Significant gaps in the literature underpinned the recommendations for future research that were also developed.
Conclusions. Based on the results of a SLR and expert opinion, seven recommendations on the use of imaging in the clinical management of OA have been recently developed by a task force of experts in the field, representing the EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis (1).

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S3:3

MANAGEMENT OF OSTEOARTHRITIS: FROM GUIDELINES UP TO THE LAST TREATMENT ISSUES

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The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published, in 2014 and revised in 2016, a treatment algorithm for the management of knee osteoarthritis (OA), which provides practical guidance for the prioritization of interventions and guides physicians to progressive, logical steps. This represents a significant advance in the preparation of recommendations for the treatment of OA, where previous guideline development has analyzed the level of evidence behind each intervention without prioritizing the interventions in a given sequence. At first step, background maintenance therapy with symptomatic slow-acting drugs for osteoarthritis is recommended, for which high-quality evidence is provided only for the prescription formulations of patented crystalline glucosamine sulfate and pharmaceutical-grade chondroitin sulfate. Paracetamol may be added for rescue analgesia. Topical non-steroidal NSAIDs may provide additional symptomatic relief. Oral NSAIDs maintain a central role in step 2 advanced management of persistence symptoms. Careful treatment selection is advocated to mitigate the risk induced by NSAIDs. Intra-articular hyaluronic acid as a next step provides sustained clinical benefit with effects lasting longer than corticosteroid injections. As a last step before surgery, the titration of sustained-release tramadol, a weak opioid, affords sustained analgesia with improved tolerability.

S3:4

MANAGEMENT: NON-PHARMACOLOGICAL ASPECTS AND UNMET NEEDS

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Osteoarthritis (OA) is a degenerative joint disorder commonly encountered in clinical practice, and is the leading cause of disability in elderly people; the aetiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes (1, 2). A number of environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways (3). Aetiological factors are also joint specific. Due to the poor self-healing capacity of articular cartilage and lack of specific diagnostic biomarkers, OA is a challenging disease with limited treatment options (3, 4).
Nonpharmacological interventions are frequently and widely used in the management of OA patients, but there is little evidence that they are effective (6, 7): the best studied and most successful nonpharmacological interventions are patient education, self-management, and exercise. There is some evidence for the pain-relieving efficacy of thermotherapy and transcutaneous electrical nerve stimulation (TENS) but not of electrotherapy, acupuncture, homeopathy, or manual therapy. The value of interventions aimed at improving function and maximizing independence (occupational therapy, walking aids, workplace adaptation) is also unclear.
Joint replacement is an effective treatment for symptomatic end-stage disease, although functional outcomes can be poor and the lifespan of prostheses is limited A variety of unmet needs ranging from the health care utilizations to specific and effective pharmacologic and non-pharmacological treatment options makes problematic a proper and effective approach to OA, despite currently available therapies and research advances (8).
Current research focuses on the development of new OA drugs; unmet needs in the treatment of chronic pain have led physicians to utilize biologic drugs in patients suffering from conditions not characterized by systemic inflammation such as osteoarthritis (OA). Current evidence does not support TNF-alpha inhibition for the management of OA, although a selected subgroup of these patients with a marked inflammatory profile may benefit from this therapy (9).
Furthermore, regenerative therapies (such as autologous chondrocyte implantation (ACI), new generation of matrix-induced ACI, cell-free scaffolds, induced pluripotent stem cells (iPS cells or iPSCs), and endogenous cell homing) are also emerging as promising alternatives as they have potential to enhance cartilage repair, and ultimately restore healthy tissue (8).
The intraarticular administration of platelet-rich plasma is evaluated as potential future therapy and has been tried in knee and hip OA with beneficial effect (10).
Consequently, it's difficult a proper clinical and therapeutic approach focusing on disease prevention, joint-preserving interventions and treatment of early osteoarthritis (11). The length of wait lists to access specialist clinics in the public system is problematic for OA patients in some countries (12).
The disease course and patient's requirements often change over time, thus requiring a periodic review and readjustment of therapy
Despite currently available therapies and research advances, there remain a variety of unmet medical needs in the treatment of OA.

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02 – Osteoarthritis and its management

OC3:1

MUTUAL INTERACTION BETWEEN OXIDATIVE STRESS AND MICRORNAS. AN IN VITRO STUDY ON HUMAN OSTEOARTHRITIC CHONDROCYTE CULTURES

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Objective. The oxidative stress and the overproduction of reactive oxygen species (ROS) play an important role in the pathogenesis of osteoarthritis (OA). Accumulating evidence demonstrated the involvement of microRNAs (miRNAs) dysregulation in the development and in the progression of many disorders, such as OA. Recently, some oxidative stress-responsive miRNAs have been identified. In this study we evaluated the effect of oxidative stress on miR-146a and miR-34a expression levels in human OA chondrocytes cultures stimulated by H2O2.
Design and Method. The chondrocytes were stimulated with H2O2 1 micromolar to induce oxidative stress. The cells were immediately processed to perform cell viability assay. The analysis of mitochondrial superoxide anion production and cell apoptosis were performed by flow cytometry. The gene expression of the antioxidant enzymes superoxide dismutase (SOD)-2, catalase (CAT), glutathione peroxidase (GPx)-4, the transcriptional factor nuclear factor erythroid 2 like 2 (NFE2L2 or NRF2) and the selected miRNAs were analyzed by qRT-PCR.
Results. The H2O2-induced oxidative stress was confirmed by the significant increase of mitochondrial superoxide anion production ($p<0.001$) and of the apoptotic ratio ($p<0.05$) in comparison to basal conditions. Furthermore, the stimulus of H2O2 significantly up-regulated the expression levels of SOD-2 ($p<0.01$), CAT ($p<0.001$) and NRF2 ($p<0.01$). A significant decrease of miR-146a ($p<0.01$) and a significant increase of miR-34a ($p<0.001$) gene expression were also observed in H2O2-stimulated chondrocytes. The same analyses were carried out after pre-treatment with taurine, a known antioxidant substance, which, in our experience, counteracted the H2O2-induced effect.
Conclusions. Our results showed the induction of oxidative stress in affecting the cell apoptosis and the expression of the enzymes involved in the oxidant/antioxidant balance. Moreover, we demonstrated for the first time the modification of miR-146a and miR-34a in OA chondrocytes subjected to H2O2 stimulus and we confirmed the antioxidant effect of taurine.

Keywords: oxidative stress, micrornas, chondrocytes.

OC3:2

KNEE ARTHRITIS AND METABOLIC SYNDROME

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Objective. The present study proposes for the first time in Constanta Country to follow the way in which the onset, the clinical manifestations and the evolution of knee arthritis are influenced by the metabolic syndrome and its components.
Design and Method. A prospective study was conducted on a group of 80 patients diagnosed with knee arthritis according to the Kellgren Lawrence classification. The analysis of demographic, clinical and biological variables was performed, with particular reference to the parameters that are part of the diagnostic criteria for the metabolic syndrome according the American Hearth Association/ National Heart, Lung and Blood Institute (AHA/NHLBI).
The data was entered into a database using Microsoft Office Excel software. Medcalc software was used to calculate the odd ratio to pinpoint the differences between patients with knee arthritis that associate or not metabolic syndrome. It was considered statistically significant a $p<0.05$.
Results. Most patients were women (85%), age 51-78 years (average age 66.07). Most of them (60%) had stage III knee arthritis. 22 patients (27.5%) was diagnosed with metabolic syndrome, 18 of whom were obese, 20 had hypertension, 20 had dyslipidemia and 22 had diabetes or only hyperglycemia.
It was observed that patients with metabolic syndrome developed knee arthritis earlier by almost 2 years. Accumulation of components of the metabolic syndrome is associated with a higher pain level and with the presence of local signs

of arthritis (p=0.0041). No significant correlations were found between the presence of the metabolic syndrome and the stage of knee arthritis.
Local signs of arthritis were associated with the diagnosis of obesity (p=0.0123) and hypertension (p=0.0161). Stiffness was associated with hypertension (p=0.0149) and diabetes (p=0.0135).
Conclusions. The association between knee arthritis and metabolic syndrome is increasingly studied and more evident. This is important for the progression of knee arthritis, but especially for preventing the onset of knee arthritis by reducing body weight, but also by proper treatment of dyslipidemia and glucidic metabolism disorders.

Keywords: knee arthritis, metabolic syndrome, prevention.

OC3:3

VISCOSUPPLEMENTATION IN NON-SEVERE KNEE OSTEOARTHRITIS: A NETWORK META-ANALYSIS OF HIGH QUALITY RANDOMIZED CLINICAL TRIALS

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Objective. To compare the efficacy of the various viscosupplementation (VS) products for the treatment of non-severe knee osteoarthritis (KOA).
Design and Method. Network meta-analysis of randomized controlled trials (RCT) with low risk of bias. Medline, Embase, and Cochrane Central were queried to identify all RCT of VS in KOA. Studies eligible were RCTs on painful non-severe KOA (Kelgren-Lawrence II-III) comparing VS with placebo or with other VS or intra-articular (IA) comparator with low risk of bias (according to Cochrane collaboration's tool). Primary outcomes were improvement in pain from baseline (VAS or WOMAC pain) and percent of OMERACT-OARSI responders at 26 weeks. Secondary outcomes were change in total WOMAC or WOMAC function, analgesic consumption, and adverse events. Continuous outcome measures were analyzed by standardized mean differences (SMD) and binary outcomes by relative risk (RR). A network meta-analysis with random effects and meta-regression was performed after exploring heterogeneity.
Results. Eighteen low risk of bias RCTs were included: 7 trials compared VS (hyaluronic acid (HA)/hylans) versus IA placebo, 3 versus IA corticoids (IA CS), and 8 versus other IA HA. The pooled analyses of all VS products (1387 patients) showed an analgesic efficacy of -.29 (SMD) versus placebo. Comparison versus IA CS showed contradictory results depending on HA molecular weight: trials of HA of Intermediate Molecular Weight (IMW) showed better analgesic response than IA CS (SMD -.87), whilst High Molecular Weight (HMW) HA did not (SMD +.19). Comparisons across HA derivatives revealed that, at 26 weeks, IMW alleviates better than Low Molecular Weight HA (LMW)(SMD -.21) but it is similar to Non-Specific Molecular Weight HA (NSMW)(SMD +.04). Hylans revealed similar analgesic effect to HMW (SMD +.06) or IMW (SMD -.09) but lower than NSMW (SMD +.15) or LMW (SMD +.28). Depending on endpoint and time frames, different effect sizes were obtained. Major safety events did not differ between VS and placebo but mild local reactions were significantly more frequent with VS.
Conclusions. Efficacy of VS is modest up to 26 weeks post-injection, and no VS seems better than others, with more expected local reactions when hylans are used.

Keywords: osteoarthritis, treatment, meta-analysis.

OC3:4

MUD-BATH THERAPY REGULATES THE EXPRESSION LEVELS OF MICRORNAS IN OSTEOARTHRITIS. EPIGENETIC CONTRIBUTION TO EXPLAIN THE MECHANISM OF ACTION OF BALNEOTHERAPY

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Objective. MicroRNAs (miRNAs) play an important role in the pathogenesis of osteoarthritis (OA); they have been detected in human plasma and in synovial fluid and are considered as potential diagnostic biomarkers and therapeutic targets of OA.
Balneotherapy is a common non-pharmacological treatment for OA patients, with a beneficial effect on pain, function and quality of life and a favourable economic profile.
The aim of our study was to evaluate the whole-blood levels of miR-155, miR-223, miR-181a, miR-146a and miR-let-7e in patients with bilateral knee OA after a cycle of mud-bath therapy (MBT).
Design and Method. Thirty-two patients with knee OA defined by the ACR criteria were included. Twenty-one patients (MBT Group) were daily treated with a combination of local mud-packs at 42°C and baths in mineral water, at 37°C for 15 minutes, for 12 applications over a period of 2 weeks, in addition to standard therapy; eleven patients (Control Group) continued their conventional treatment alone.
Global pain score was evaluated by Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscores and miRNA expression were evaluated at baseline and after 2 weeks. Peripheral whole-blood was collected into PAXgeneTM Blood RNA tubes, stored a -80°C and total RNA was extracted. The expression of miR-155, miR-223, miR-181a, miR-146a and miR-let-7e was determined by qRT-PCR.
Results. A statistically significant improvement of clinical parameters and a significant decrease of miR-155, miR-181a, miR-146a (p<0.001) and miR-223 (p<0.01) expression levels were observed after MBT. No clinical and biochemical modifications were detected in the Control Group. No significant variations of miR-let-7e were shown in both studied groups after 2 weeks.
Conclusions. Our data showed that MBT can modify the expression of miR-155, miR-181a, miR-146a and miR-223, that are up-regulated in OA. It could be due to the heat stress and the hydrostatic pressure, since some miRNAs were found to be temperature and mechano-responsive.
However, further studies are needed to better explain the mechanism of action of MBT and the role of miRNAs in OA.

Keywords: micrornas, balneotherapy, osteoarthritis.

OC3:5

PATIENTS PERCEPTION OF PAIN IN OSTEOARTHRITIS: RESULTS OF A ROUMANIAN SURVEY

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Objective. Background: Osteoarthritis (OA) treatments are mainly based on analgesia and physical therapies, but patients usually still experience pain and this will impact quality of daily living.
Objectives: Pain perception was evaluated in a cohort of patients with osteoarthritis.
Design and Method. 75 patients with osteoarthritis were enrolled in this study. All patients signed an informed consent approved by local ethic committee. We collected data about demographics, clinical exams, joint involvement and treatment. All patients completed a HAQ evaluation and a Visual Analogue Scale (VAS) for pain (0-10). Patient perception about osteoarthritis symptoms and the disease impact upon there life were captured in a questionnaire. They were asked if pain interfere with usual activity (work, preparing meal, house kipping) or with social activity (family interaction, friends) or how they perceived pain or efficacy of the treatment in the last month. Statistical analysis was made with SPSS.
Results. Mean age at evaluation was 63 with a female predominance (83%). 89.3% were taking NSAIDs and 73.3% acetaminophen in the last five days. Despite treatment, VAS for pain was at least 5 for more than 80% of patients. Higher VAS was significant more frequent in female patients (p 0.001), in patients with family history of osteoarthritis (p 0.023) and in the one with sedentary life style (p 0.035). Most of the patients considered that pain interfere with daily activity, the impact being evaluated as moderate for 46.67% of patients and severe for 32%. Pain also had a negative impact on their social life, the percentage for moderate disturbance being of 38.67% and 18.67% for severe one. Only 11% of patients consider that the pain control is well managed. 40% of the patients do not expect that there quality of life will improve in the future.
Conclusions. Residual pain after treatment is present in most of the patients with osteoarthritis. Persistent pain interferes significantly with daily living and quality of life, but also contributes to a resumption of these patients when it comes to expectation to a pain free life.

Keywords: pain, patient perception, osteoarthritis.

OC3:6

KNEE EXTENSOR MUSCLE WEAKNESS AND RADIOGRAPHIC KNEE OSTEOARTHRITIS PROGRESSION

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Objective. Knee extensor weakness (KEW) is a modifiable risk factor for the development of radiographic knee osteoarthritis (KOA); However, it does not appear to increase the risk of radiographic KOA progression. The relationship between KEW and disease progression may depend on the local mechanical environment. The objective of this study is to determine whether KEW is associated with radiographic (medial and/or lateral) knee osteoarthritis (KOA) progression and how this relationship differs depending on frontal plane knee alignment and sex.
Design and Method. We studied 3,075 knees (1,961 participants, 58% female) from the Osteoarthritis Initiative with radiographic Kellgren/Lawrence grade 1-3. Peak KE torque (Newton metres per body mass) was assessed at baseline, and progression defined as fixed-location joint space width loss (>= 0.7mm) in the medial and lateral tibiofemoral compartments from baseline to 4-year follow-up. Knee-based generalized estimating equations, stratified by alignment (malaligned vs. neutral), estimated the odds of progression for those in the lowest (and middle) vs. highest tertile of KE torque. Secondary analyses explored whether this relationship was compartmental- or sex-specific.
Results. Being in the lowest (or middle) compared with the highest torque tertile increased the odds of progression in neutrally aligned knees (odds ratio [OR] 1.29 [95%CI 1.01, 1.68] and 1.33 [1.03, 1.71], respectively), but not after adjusting for age, sex, body mass index (BMI), pain and radiographic severity. In secondary analyses, women with neutral alignment in the lowest compared to the highest torque tertile had significantly increased odds of lateral compartment progression independent of age, BMI, disease severity and pain (OR 1.48, 95%CI 1.06, 2.24). No association was observed between KE torque and KOA progression in men, irrespective of alignment.
Conclusions. In the tibiofemoral joint of men and women as a whole, lower KEW is generally not associated with KOA progression over four years, particularly after adjustment for other risk factors. However, in unravelling this relationship further, this study has identified an important subset of women (without malalignment), in which KE weakness was associated with (lateral) tibiofemoral progression.

Keywords: osteoarthritis, knee, muscle, strength.

03 – Pediatric Rheumatology in the Mediterranean area

PED1:1

DIFFERENCES IN DISEASE PHENOTYPE, MANAGEMENT AND OUTCOMES OF CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS THROUGHOUT THE WORLD – ANALYSIS OF 8,325 PATIENTS ENROLLED IN THE EPOCA STUDY

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Background. Several epidemiologic surveys have documented a remarkable, yet unexplained, disparity in the prevalence of juvenile idiopathic arthritis (JIA) subtypes among different geographic areas or ethnic groups. Moreover, the therapeutic approach to JIA is not standardized and the availability of the novel and costly biologic medications is not uniform throughout the world. This disparity may have significant impact on disease outcome. The multinational study of the EPidemiology, treatment and Outcome of Childhood Arthritis (EPOCA study) is aimed to obtain information on the variability of JIA phenotypes in different geographic areas, the therapeutic approaches of pediatric rheumatologists practicing in diverse countries, and the disease status and outcome of children with JIA currently followed worldwide.
Methods. Participation in the study was proposed to all pediatric rheumatology centers that are part of the Pediatric Rheumatology International Trials Organization (PRINTO), and to several centers in the US and Canada. Each center was asked to enroll 100 consecutive JIA patients or all consecutive patients seen within 6 months. Each patient received a retrospective and cross-sectional assessment. Parent- and child-reported outcomes were recorded through the administration of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Participating countries were grouped into 6 geographic areas. Patients were then grouped according to their country's gross domestic product per capita (GDP) and the total expenditure on health per capita (HE) (source www.who.org).
Results. Currently, 8,325 patients from 44 countries have been entered in the web database. Comparison of main epidemiology, treatment, and outcome features across the different geographic areas is presented in the table. Patients living in countries with GDP or HE below the median had lower frequency of remission, higher median cJADAS, higher frequency of damage, and were less frequently prescribed biologic DMARDs. These results were confirmed when analyses were conducted only in oligoarthritis or polyarthritis patients.

	Africa N = 261	Asia N = 874	Eastern Europe N = 2587	Latin America N = 814	North America N = 422	Western Europe N = 3367
Median (IQR) age at onset, years	7 (3.6-10.5)	5.7 (2.9-9.2)	6.4 (2.9-10.5)	6.6 (3.6-10.3)	8.1 (3.7-11.1)	4.1 (2-8.7)
Systemic arthritis	17.2	26.5	8.1	17.7	4.7	6.9
Oligoarthritis	23	31.9	44.1	31.7	33.9	49.2
Uveitis	4.6	5.5	10	6.6	10.4	16.9
Use of biologics	22.6	23.6	28.9	34.2	47.6	39
Median (IQR) cJADAS10	7 (2-11)	2.5 (0-7.8)	4.5 (1-9.5)	2.5 (0-9.5)	2.3 (0-7)	2 (0-6)
Median (IQR) JAFS score	4 (0-8)	1 (0-5)	1 (0-4)	1 (0-5)	1 (0-4)	0 (0-3)
JADI-Articular > 0	27.6	19.2	23.7	31.9	15.2	12.2
JADI-Extraarticular > 0	24.5	16.8	14.8	14.5	5.9	9.1

Data are percentages unless otherwise indicated. cJADAS: clinical (3-item) JADAS; JAFS: Juvenile Arthritis Functionality Scale; JADI: Juvenile Arthritis Damage Index
Conclusions. These results provide further evidence of the wide difference of JIA characteristics across geographic areas in terms of age at disease onset, subtype prevalence, and frequency of anterior uveitis. Overall, patients living in non-Western countries had higher levels of disease activity and cumulative damage than patients followed in North America and Western Europe. This disparity in disease outcomes may be partially due to differences in the availability or affordability of biologics.

PED1:2

LONGITUDINAL EVALUATION OF GROWTH AND PUBERTY DEVELOPMENT IN PEDIATRIC RHEUMATIC DISEASES

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Purpose. Children represent a small fraction of systemic lupus erythematosus (SLE) and dermatomyositis (DM) patients. Compared to adult onset SLE and DM, the juvenile counterpart are in general considered more severe, resulting in more intensive treatment and higher morbidity/mortality. Growth failure and delayed puberty are unique features of the juvenile form of SLE and DM often caused by long-term disease activity, side effects of drugs especially corticosteroids, and/or co-morbid conditions. Delayed growth and puberty may result in irreversible damage, affect the patients' quality of life and add to the burden of coping with a chronic disease. During the last decades, prognosis is greatly improved and now the goal for the patients is to grow and mature sexually into adulthood, with minimal loss of their physical, emotional, and genetic potential. Due to the rarity of the disease and lack of large-scale cohort studies, knowledge of growth and pubertal development in children is limited. The risk of growth failure and delayed puberty are special problems of the childhood rheumatic diseases, and the consequences are lifelong. Prospective long-term follow-up studies are few, and there is very limited knowledge on growth and puberty in children with pediatric rheumatic conditions. This presentation will review the current state of the art for the evaluation of longitudinal data on growth and puberty in a large- scale cohort of juvenile SLE and DM from studies conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO).
Methods. Data from juvenile SLE or juvenile DM≤18 years in active phase, with anthropometric data available at four follow-up visits over two years, were studied.

Results. A total of 331/557 (59.4%) juvenile SLE and 196/275 (71%) juvenile DM were included. There was a significant reduction in parent-adjusted height z score with time in either gender and diseases with male height being most affected in juvenile SLE.
Median BMI z score peaked at 6 months and was still significantly above baseline after 24 months with no gender difference in either diseases.
Juvenile SLE females with onset age <12 years had a median parent-adjusted height z score of -0.87 with no catch-up growth; similarly juvenile DM females with a disease duration ≥12 months after onset had significantly lower parent-adjusted height z score and no catch-up growth.
At the end of the study, growth failure was seen in 14.7%-21 of the females and 24.5%-15% of the males in juvenile SLE and DM respectively.
Height deflection (less than -0.25/year) was found in 20.7%-25% of the females and 45.5%-31% of the males in either diseases.
Delayed pubertal onset was seen in 15.3%-36% and 24%-41% of the females and males, respectively in either disease.
For juvenile SLE growth failure baseline determinants were previous growth failure (OR: 56.6), age at first visit _13.4 years (OR: 4.2) and cumulative steroid dose >426 mg/kg (OR: 3.6). In JDM the children with recent onset of puberty or previous growth failure, have the highest risk of delayed pubertal development and further growth retardation
Conclusions. The children at risk of suffering a negative effect on height and pubertal development, are pre- and peripubertal children.

04 – FOURTH SESSION: Autoinflammatory and Rare Connective Tissue Diseases

S4:1

AUTOINFLAMMATORY DISEASES: DIAGNOSTIC CRITERIA, GUIDELINES AND ADVANCES

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Autoinflammatory diseases are a group of inflammatory conditions secondary to an exaggerated activation of the innate immunity in response to exogenous or endogenous stimuli, in the absence of high-titer autoantibodies. The first conditions identified were characterized by recurrent episodes of inflammation and fever separated by periods of general wellbeing, defined as recurrent fevers. Most of these conditions recognize a genetic cause. Familial Mediterranean Fever (FMF) secondary to mutations of MEFV (MEditerranean FeVer) gene. Mevalonate kinase deficiency (MKD, AR) caused by autosomal recessive mutations of mevalonate kinase (MVK) gene coding for an enzyme involved in the cholesterol biosynthesis. Tumor necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS) an autosomal dominantly inherited (AD) disease secondary to mutations of type I TNF receptor (TNFSRF1A). Cryopyrin-associated periodic syndromes (CAPS) are a group of disorders ranging from a milder phenotype with recurrent episodes of fever, urticarial rash and arthralgia/arthritis to a severe chronic infantile multisystemic inflammatory disease (defined as chronic infantile cutaneous neurological articular, CINCA) associated to heterozygous mutations of NLRP3. Besides these inherited disorders, similar recurrent fever episodes can be also observed in a relatively frequent multifactorial autoinflammatory disease, named PFAPA (periodic fever, aphthosis, pharyngitis and adenitis) syndrome, characterized by regular fever episodes variably associated to at least one of the three manifestations in the acronym in the absence of signs of infection. A number of clinical diagnostic and classification criteria have been proposed for all HPF and PFAPA. Beside, a general confusion in the use of the terms “diagnostic” and “classification” criteria, these criteria were uniquely based on the prevalence of the clinical manifestations observed during the fever episodes in each condition. Due to the general overlap of the clinical manifestations observed in the five different conditions, most of these criteria displayed a general low accuracy when tested in populations in which all the different conditions are present (ref). Moreover, none of the criteria available in literature takes into account the results of the genetic analysis that per se, should be considered pathognomonic at least in the presence of a confirmatory genotype. In this manuscript, we present the final results of a project aimed to obtain a large a consensus on the development of novel, more sensitive and specific classification criteria for FMF, MKD, TRAPS, CAPS and PFAFA. This project was based on a consensus formation technique among clinicians and geneticists working in the field and data validation in the large dataset of patients extracted by the real world, thorough the EUROFEVER Registry.
A multistep process, based on a combination of expert consensus and analysis of real patient data, was conducted. A panel of experts (clinicians and geneticists) was first asked to classify 360 patient profiles as having or not one of the four HRF (FMF, TRAPS, MKD, CAPS) or PFAPA, based on clinical, genetic and laboratory features collected in the Eurofever registry. The 360 patients comprised 60 patients for each genetic condition (with different genotypes), 60 PFAPA patients and 60 patients with undifferentiated autoinflammatory disease with recurrent fever. Next, the ability of candidate criteria to classify individual patients for each disease was assessed by evaluating the agreement between the classification yielded by the criteria and the consensus classification of the experts. The final criteria were selected in a consensus conference.
Experts achieved consensus on the classification of 281/360 (87%) patient profiles. A total of … candidate criteria were tested *in silico* for the five conditions. The best performing criteria and criteria obtained from the literature were evaluated in the consensus conference. During the conference, experts arrived to a consensus on 2 sets of criteria for each HRP, one including genetic and clinical variables, the other with clinical variables only. A clinical criteria for PFAPA was also selected. In cross-validation analyses, on a separate set of 1110 patient with recurrent fevers these criteria displayed a high sensitivity and specificity. In conclusion, we have developed a set of classification criteria for HPF and PFAPA and provided preliminary evidence of their construct validity. Prospective validation is required to confirm the high accuracy of the criteria.

S4:2

FOCUS ON FAMILIAL MEDITERRANEAN FEVER

H. Lachmann

Familial Mediterranean fever (FMF) is by far the most common of inherited autoinflammatory diseases. It is recognised worldwide but is most prevalent in the Eastern Mediterranean.
The symptoms of FMF are recurring attacks of fever and serositis lasting 12 to 72 hours. Peritonitic abdominal pain occurs in 80% of attacks. Pleuritic chest pain is seen in 15-30% of the patients. Acute non-erosive arthritis, usually affecting one or two large joints of the lower limb or the sacroiliac joints is seen rarely. An erysipelas-like erythema during attacks is seen in about 25% of pediatric cases and can be associated with arthritis. There is a brief marked inflammatory response during an attack and subclinical inflammation is common between attacks. A variety of diagnostic criteria for adults and children have been published but few have been fully validated in atypical populations.
Mutations in MEFV, a 10 exon gene located on chromosome 16, were found to be associated with FMF in 1997. The gene encodes a 781 amino acid protein, pyrin and more than 310 MEFV sequence variants have been reported although not all are associated with a disease phenotype. The majority of patients have two mutations but up to 20% of patients are reported to be heterozygote. A few mutations are associated with genuinely dominant inheritance, particularly in atypical populations. The most frequently seen pathogenic variants are located in exon 10 and M694V is both the most common and the most severe. Evidence-based recommendations have been developed for the use of genetic testing in the diagnosis of FMF by the Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE) initiative.
Current evidence suggests that, unusually for a recessive disease, mutations are gain of function. Pyrin is activated when dephosphorylated at Ser208/Ser242 allowing microtubular interactions which are critical for formation of the pyrin inflammasome and activation of caspase 1. Mutations appear to result in reduced binding of RhoA effector kinases, decreased phosphorylation of pyrin resulting increased inflammasome formation and production of IL-1β. The carrier frequency, of up to one in five in high risk populations, has long fuelled speculation that the FMF trait may have conferred a survival benefit. Pyrin appears to act as an indirect sensor of a variety of bacterial toxins, providing a potential mechanism by which activating mutations could augment the innate immune response.
One of the most remarkable features of FMF is that a disease characterised by recurrent severe attacks of multisystem inflammation does not result in serious long-term complications more often.
The recurrent inflammatory attacks in FMF cause intense acute symptoms and confer a markedly increased relative risk of developing AA amyloidosis and eventually end stage renal disease. Prior to the colchicine era this was a major cause of early mortality. Other potential complications of FMF include destructive arthritis, adhesions, subfertility and vasculitis. Fortunately these remain very rare and, with long-term prophylactic treatment, recent studies suggest that both the complications and mortality for FMF appear to match that of healthy controls.
Recent EULAR guidelines have been published on the management of FMF. The treatment of FMF is lifelong colchicine. It is important to explain that it is only effective as long-term prophylaxis and that colchicine provides little useful analgesia in acute attacks. On appropriate doses most patients will be symptom-free and the risk of amyloidosis almost completely disappears. Children usually need a higher dose per kilogram than adults. Cohort studies suggest that colchicine in pregnancy is safe and should not be discontinued. IL-1 inhibitors have been demonstrated in trials to be effective therapy in resistant cases and canakinumab was licenced for this indication in 2017 as a result of the CLUSTER study.

S4:3

GENETIC, EPIGENETIC AND ENVIRONMENTAL FACTORS AND THE VASCULITIS RISK IN THE MEDITERRANEAN

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Purpose. To discuss the potential role of genetic, epigenetic and environmental factors on the risk of particular vasculitis forms in the Mediterranean region compared to other parts of the world.
Methods. Articles published in English were searched through PubMed to collect information on the increased prevalence of particular forms of vasculitides in the Mediterranean region and also on the possible etiological factors, including genetic, epigenetic factors and diet.
Results. Two forms of systemic vasculitis, namely Behçet disease and Takayasu arteritis are known to be relatively more common in the Mediterranean region, and genetic factors are possibly playing the most critical role in this peculiar prevalence features in this part of the world. Behçet disease is strongly associated with HLA-B*51 and Takayasu arteritis with HLA-B*52, and distribution of especially B*51 shows a geographic preference for the Mediterranean region, reaching up to 29% in Turkey. Non-HLA genetic factors are also contributing to these epidemiological factors, and it is especially true for the penetrant MEFV mutations, which are responsible for autosomal recessively inherited autoinflammatory Familial Mediterranean Fever (FMF), and p.Meth694Val and other penetrant exon 10 variants affect the risk for vascular inflammation in the region. The prevalence of heterozygous carriers of the MEFV gene exon 10 variations in healthy Mediterranean population is relatively high and beyond the definition of pathogenic mutations. These penetrant variants are known to be associated with an increased risk for various forms of vasculitis, especially for classical polyarteritis nodosa, Henoch Schönlein purpura and Behçet disease. Similarly, another autosomal recessively inherited inflammatory disorder known as Deficiency of Adenosine Deamimase 2 (DADA2) and associated with variations in the CECR1 gene, was also first described in juvenile polyarteritis nodosa families of Meditterranean origin. Regarding the increased prevalence of healthy carriers, an heterozygous advantage associated with the MEFV variants in this part of the world has long been discussed, and a better survival in the past in patients with tuberculosis or during plague and smallpox epidemics has been suggested as a possible explanation for this genetic drift. Other environmental factors, especially diet may have a potential role to induce epigenetic changes, which may affect the expression of genetic variants and hyperinflammatory features in the innate immune system leading to vasculitic manifestations, but available data is limited to guide patients with systemic vasculitis.
Conclusions. Genetic factors play an important role in the increased prevalence of Behçet disease and FMF/MEFV associated vasculitic syndromes in the Mediterranean region, and the potential effects of dietary and other environmental modifications on the epigenetic changes warrant further investigations for controlling hyperinflammatory innate response and increased vasculitis risk.

S4:4

FOCUS ON BEHÇET'S DISEASE

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Behçet's syndrome (BS) is a multisystemic inflammatory disorder classified among primary vasculitis. The diagnosis is based on clinical signs due to the lack of specific tests. Typical clinical manifestations include oral and genital ulcers, uveitis, and skin lesions. The involvement of central nervous system, vessel tree and gastrointestinal tract even if less frequent can be life threatening. The disease is characterized by a relapsing-remitting course with a period of substantial well-being between the phases. BS mainly affects young (20-40 year-old) males, but no age is spared. The male to female ratio varies from ca. 3:1 to 1:1 with equal male to female ratios being reported from the US and Europe. Its prevalence greatly varies in different countries This disorder shows a particular geographic distribution with a high prevalence in areas of the world extending between 30° and 45° north parallel from the Mediterranean basin to the Asia. This peculiar geographic distribution, corresponding to the historical "Silk Road", is most probably due to the association of environmental factors together with genetic markers of susceptibility. Between the different etiologic factors so far studied the HLA B51 antigen seems to be more closely linked to the disease susceptibility. BS usually occurs in sporadic form but familial cases have been described. The hallmark of BS is recurrent oral and often genital aphthosis. A variety of skin lesions can be observed in 80% of patients with BS, although only one-quarter of patients have cutaneous changes at onset. Half of patients have papulopustular lesions, while pseudofolliculitis and erythema nodosum are less frequent. Acneiform lesions are much less common and should be differentiated from adolescent acne and glucocorticoid-related acne. Other infrequent cutaneous abnormalities are pyoderma gangrenosum, erythema multiforme, and cutaneous ulcers. Inflammatory ocular involvement is quite common in patients with BD. Approximately 60% of patients with BD had eye disease characterized by anterior uveitis, posterior uveitis/retinal vasculitis, or both. Posterior uveitis/retinal vasculitis occurs more often in males than in females and carries a worse prognosis than anterior uveitis. About half of patients have joint manifestations, which are among the presenting features in 14-18% of cases. The typical pattern is of a mono- or oligoarthritis, with the knees and ankles being most commonly affected. In most cases, BS-associated arthritis is non-erosive and does not lead to articular deformities. About one-fifth of patients develop neurological manifestations, usually some years after the onset of BS. Parenchymal brain disease, often referred to as "neuro-Behçet", is typically characterized by a meningoencephalitis mainly involving the deep hemispheres and brainstem. Commom manifestations of Neuro-Behçet include headache, bilateral pyramidal signs, hemiparesis, behavioral changes, and sphincter alterations. Neuro-Behçet should be distinguished from the rare intracranial hypertension syndrome secondary to thrombophlebitis of the dural sinuses. Magnetic resonance imaging is the key investigation to clinch the diagnosis of Neuro-Behçet or thrombophlebitis of the dural sinuses. Vascular lesions arise in approximately one-third of patients with BS, but are infrequent as initial manifestations. The commonest type of presentation is superficial and deep thrombophlebitis preferentially involving the lower limbs. Arterial aneurysms (mainly of the pulmonary arteries) occur rarely; they prevalently affect young males, and carry a high risk of rupture. There are no pathognomonic tests for BS. The International Study Group for Behçet disease (ISGB) criteria are those most widely used to classify BS (Table I). The ISGB criteria are highly specific, but have limited sensitivity to diagnose early BS. Therefore, although they were originally defined "diagnostic", they should not be used to diagnose BD at the individual patient's level. Inflammatory markers, such as the erythrocyte sedimentation rate and C-reactive protein, are elevated in only 15% of patients with BS, mainly those with vascular manifestations. Therefore, they have poor sensitivity for BS, besides, they are nonspecific. The pathergy test is probably the most specific test available to diagnose BS. It consists of the intradermal injection of the skin with a 20-gauge needle under sterile conditions; it is considered positive if an erythematous sterile papule develops within 48 hours. The pathergy test is positive in normal subjects and other disorders characterized by neutrophil hyperreactivity such as Sweet's syndrome. However, the sensitivity of the pathergy test in BS is rather low, being in the range of 11-50%.
The treatment of BS often require a multidisciplinary. Treatment should be individualized according to age, gender, type and severity of organ involvement and patient's preferences with the aim to reduce inflammation process, improve quality of life, prevent disease's relapses and development of irreversible and severe organ damage. C-DMARDs are widely used in the treatment of BS however biological agents (antagonists of TNFalpha, IL-1, IL-6) have been found effective in severe and refractory cases. EULAR recommendations for the treatment of BS have been recently updated.

Table
International Study Group Criteria for the diagnosis of Behçet's disease
In the absence of other clinical explanation, patients must have:
1. Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in one 12-month period and two of the following:
2. Recurrent genital ulceration
3. Eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination or retinal vasculitis observed by an ophthalmologist
4 Skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules in postadolescent patients not on corticosteroids
5. Pathergy, read by a physician at 24-48 hours

S4:5

ERN ReCONNET, EUROPEAN REFERENCE NETWORK ON RARE AND COMPLEX CONNECTIVE TISSUE AND MUSCULOSKELETAL DISEASES: FIRST YEAR ACTIVITY

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European Reference Networks (ERNs) are networks involving healthcare providers across Europe. Their aim is to tackle rare and complex diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources. The European Reference Network for rare and complex connective tissue and musculoskeletal diseases ERN ReCONNET involves 26 HCPs from 8 different EU countries and covers the following diseases: Systemic Sclerosis, Mixed Connective Tissue Diseases, Idiopathic Inflammatory Myopathies, Anti-phospholipid syndrome, Undifferentiated Connective Tissue Diseases, IgG4 related diseases, Relapsing Polychondritis, Systemic Lupus Erythematosus, Sjögren Syndrome, Ehlers Danlos Disease.
The aim of the ERN ReCONNET is to develop a framework for the delivery of high quality, innovative, sustainable and equitable standard of care and practice for better access to care of European patients.
The annual work plan for the first year (March 2017 - February 2018) has been to establish a community to enhance transnational cooperation between different groups (healthcare providers, patients, caregivers and families, stakeholders, etc.) to develop a comprehensive and harmonized approach to rare and complex autoimmune and hereditary connective and musculoskeletal diseases (rCTDs).
The scientific activities of the first year were mainly focused on the identification of existing recommendations and or clinical practice guidelines (CPGs) on the diseases covered by the network. This work allowed to identify CPG for many of the diseases covered by ERN ReCONNET, as well as unmet needs, in particular for the rarest diseases (IgG4 related diseases, relapsing polychondritis, mixed CTD). In addition preliminary work to co-design the website was started involving all Networks stakeholders.
In conclusion, the ERN ReCONNET will significantly improve the clinical approach to rare and complex CTDs, promoting an improvement of the quality of the specialized care provided to patients, of the activity of the physicians, the empowerment of the patients sharing expertise and promoting the interaction among EU HCPs.

05 – Autoinflammatory and Rare Connective Tissue Disease

OC4:1

A GENETIC COHORT STUDY TO GENOTYPE SEVERAL INTERLEUKIN GENE POLYMORPHISMS IN A GROUP OF BEHÇET'S SYNDROME PATIENTS LIVING IN THE MEDITERRANEAN AREA

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Objective. The aim of our study was to investigate the mutational state of several interleukin (IL) genes in order to describe their frequency in a group of Italian Behçet's syndrome (BS) patients. The interleukins are key components of the immune-regulatory pathway. Despite the dysregulation of the immune response has been related to the onset and development of BS, the disease etiology remains unclear, however it is related to both genetics and environmental factors. The BS genetic background was investigated in genome-wide association studies (GWASs) and various risk loci were reported. Previous data has highlighted an association of IL gene single nucleotide polymorphisms (SNPs) with BS susceptibility among BS-related genes.
Design and Method. We recruited 61 consecutive BS patients living in the Mediterranean area (mean age ± SD: 46.78±12.76; sex ratio: 37 males/24 females) fulfilling the ISG criteria. Genomic DNA was isolated from patient's whole blood using standard procedures. Five IL tagSNPs (IL10 rs1518111 and rs1800872, IL23R-IL12RB2 rs924080, IL23R rs17375018, IL12A rs17810546) were genotyped after a primer design bioinformatics step using an NCBI Primer-Blast tool. Positive and negative controls were used in the PCR amplification. Good-quality amplicons were sequenced by the GATC Biotech Sanger sequencing service. SNPs analysis and their functional effects were performed using bioinformatics tools (BlastN and Mutation Surveyor).
Results. Table I shows IL polymorphisms distribution. IL tagSNPs genotypes highlighted a frequency of IL10 rs1800872 mutant CC genotype (57.38%) than wild-type AA genotype (18.03%); the heterozygous genotype (AC) was identified in 15/61 patients (24.59% of cases). No difference was found when wild-type AA genotype and mutant GG genotype frequencies of IL10 rs1518111 were compared. Higher frequencies of wild-type genotype compared to both heterozygous and homozygous mutant genotype for IL23R-12RB2, IL23R and IL12A SNPs were also found.

Table

GENE	*SNP ID*	*GENOTYPE*	*BS PATIENTS* n (%)
IL10	rs158111	AA AG GG	24 (39.34) 14 (22.95) 23 (37.70)
IL10	rs1800872	AA AC CC	11 (18.03) 15 (24.59) 35 (57.38)
IL23R-12RB2	rs924080	TT TC CC	35 (57.38) 22 (36.07) 4 (6.56)
IL23R	rs17375018	GG GA AA	36 (59.02) 19 (31.15) 6 (9.84)
IL12A	rs17810546	AA AG GG	51 (83.61) 3 (4.92) 7 (11.48)

Conclusions. The data shows a frequency of IL rs1800872 mutant genotype higher than the other IL SNPs, supporting the major role of this variant in influencing BS susceptibility. Going forward, analyses of a larger cohort of patients and matched controls are needed to confirm this preliminary data.

Keywords: Behçet syndrome, interleukin, single nucleotide polymorphism.

OC4:2

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS IN

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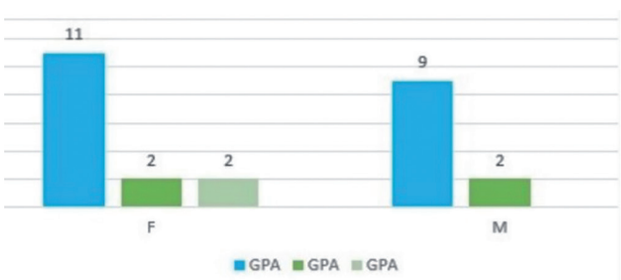
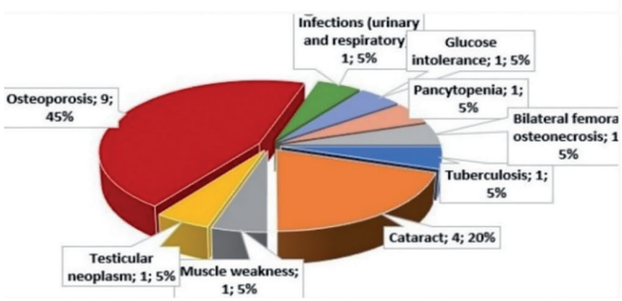
Objective. Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) represent a group of conditions evolving with necrotizing inflammation in small and medium-sized blood vessels. AAV are composed of GPA (granulomatosis with polyangiitis, former Wegener's granulomatosis), MPA (microscopic polyangiitis) and EGPA (eosinophilic granulomatosis with polyangiitis, former Churg-Strauss syndrome). AAV receive immunosuppressive therapy associated with a high risk of complications.
The aim of this study was to characterize a single center cohort of AAV patients regarding clinical, biological and therapeutic features.
Design and Method. We realized a cross-sectional study by consequently enrolling all the patients registered with AAV diagnosis between 2009 and 2017 in Department of Rheumatology of "Sfânta Maria" Hospital. Demographic, disease-related and therapeutic-related parameters were collected. The data was extracted from the clinical files.





Results. The study sample included 26 cases, 15 females and 11 males: 20 patients GPA, 4 MPA and 2 cases EGPA. Mean age at the time of diagnosis was around 48 but 12 patients presented delays between age at the onset and age at the time of diagnosis (the mean delay was 2 years). The most frequent clinical manifestation identified where pulmonary, musculoskeletal and renal. 15 patients had a diagnostic biopsy performed. ANCA detection revealed 16 cases of c-ANCA and 7 cases of p-ANCA and 11 patients presented other positive serology. A combination of glucocorticoids and cyclophosphamide was used in most of the cases for remission-induction treatment and the same scheme was used for relapse cases. For maintenance phase a combination of glucocorticoids and azathioprine was preferred. 13 patients (50%) developed treatment related complications.
Conclusions. Most of the patients were diagnosed with GPA (20) and the least were diagnosed with EGPA (2). Biopsy was performed in 15 cases and it was mostly nasal. For remission-induction prevailed the combination of glucocorticoids and cyclophosphamide. Most treatment related complications were due to glucocorticoids administration. Osteoporosis was predominant.

Keywords: vasculitis, ANCA, granulomatosis.

OC4:3

CAN AUTOANTIBODIES PREDICT OUTCOMES OR SURVIVAL IN INTERSTITIAL LUNG DISEASE?: RESULTS FROM A RETROSPECTIVE COHORT STUDY IN GREECE

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Objective. Few studies have so far questioned the role of autoantibodies (AAbs) in determining the prognosis of patients with interstitial lung disease (ILD) and present contradictory results. The present retrospective study aimed to investigate whether positive AAbs have any impact on survival and time evolution of radiological findings and pulmonary function in ILD.
Design and Method. Medical charts of patients with ILD followed up in a rheumatology and a respiratory outpatient clinic were retrospectively reviewed. Patients with regular clinical, functional and computed tomography (CT) imaging follow-up for at least 12 consecutive months and complete testing for a panel of AAbs were selected for further analysis. Eligible patients were classified into two groups according to the presence [ILD/AAb(+)] or absence [ILD/AAb(-)] of positive ANAs and/or other specific AAbs. Serial measurements of forced vital capacity [FVC (% pred.)] and single-breath diffusion capacity [DLCOSB (% pred.)], baseline and follow-up high resolution CT findings and survival data were also recorded. All-cause mortality and longitudinal indicators of ILD progression (decrease from baseline in absolute FVC of equal/greater than 10% or absolute DLCOSB of equal/greater than 15%) were the primary study outcomes. DLCOSB <40% predicted on at least two consecutive measurements and progression of hrCT findings were our secondary endpoints.
Results. Two hundred and six patients with ILD were initially screened and 94 met the inclusion criteria. Sixty nine of them were classified as ILD/AAb(+), while 49 fulfilled criteria for a specific CTD. ILD/AAb(+) patients were predominantly female (71% vs 32%), were significantly younger and had longer duration of follow-up (78.1±53.1 vs 41.6±26.7 months), compared with ILD/AAb(-) patients (p<0.01 for each comparison). At the end of follow-up, mortality rates and the percentage of patients with a sustained FVC decrease or high-grade dyspnea were lower in the ILD/AAb(+) group (p<0.05). With the exception of DLCOSB <40% pred., cox proportional hazards models were statistically significant for each of the other study endpoints in favor of the ILD/AAb(+) group (p<0.05 for each comparison).
Conclusions. Among patients with ILD, presence of positive AAbs is associated with a more favorable prognosis in terms of mortality, pulmonary function decline and radiological progression.

Keywords: interstitial lung disease, autoantibodies, outcome.

OC4:4

BIRMINGHAM VASCULITIS ACTIVITY INDEX (BVAS) A USEFUL TOOL IN ASSESSING DISEASE ACTIVITY IN BEHÇET'S DISEASE

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Objective. The main objective was to compare two vasculitis activity scores (Birmingham Vasculitis Activity Score, Behçet's Disease Current Activity Form 2006) applied to a group of patients diagnosed with Behçet's Disease and establish correlations between them, damage and the need for immunosuppressive therapy.
Design and Method. A study was performed on a cohort of patients diagnosed with Behçet's Disease according to The International Criteria for Behçet's Disease (ICBD) under surveillance in one Rheumatology Centre, from a non-endemic area. Vasculitis activity (BVASv3, BDCAF2006) and damage (VDI) scores were calculated for each patient.
Results. The study enrolled 20 patients. The mean age at the time of the diagnosis was 35.7 years ± 10.5years standard deviation (SD). 14 (70%) patients were under the age of 40, with a male predominance 60% (12 patients). Active disease was present in all selected cases at the time of the diagnosis. Spearman's rank correlation coefficient between BVAS v3 and BDCAF was strong r=0.862 and statistically significant p<0,001. The outcome analysis after remission was calculated and rank correlation coefficient between VDI, and both BVASv3 and BDCAF was moderate (VDI-BVASv3 r=0.747, p<0.001, VDI- BDCAF r=0.795, p<0.001). As for immunosuppression induction decision and activity scores, the correlation coefficient was moderate (r=0.734 for BVASv3, r=0.647 for BDCAF) with p<0.001. A moderate correlation was observed between immunosuppressive treatment and VDI (r=0.700, p<0.001). The cause of damage (*i.e.* vasculitis vs. treatment) is not taken into consideration when we calculate VDI. Data analysis showed the presence of mild correlation and no statistical impact between cyclophosphamide treatment duration and damage calculated as VDI (r=0.472, p=0.36). In contrast, when rank correlation coefficient between cortisone therapy and VDI was calculated, a moderate statistical impact was observed (r=0.609, p<0.001).
Conclusions. Using Disease activity indexes, an objective assessment of disease's activity can be obtained. A moderate to strong correlation was observed between activity indexes, decision to start immunosuppressive treatment and damage progression. Comparing the two activity indexes, it resulted that: BVASv3 correlates stronger with physician's decision to initiate immunosuppressive treatment and both of them are equally able to anticipate damage.

Keywords: Behçet, activity score, immunosuppression.

OC4:5

A SEASONAL ONSET FOR POLYMYALGIA RHEUMATICA?

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Objective. Polymyalgia rheumatica (PMR) is an inflammatory disorder of the elderly characterized by girdle pain and stiffness, constitutional symptoms and elevation of inflammatory indexes. Data on seasonality of onset of PMR and of its companion disease, giant cell arteritis (GCA), are controversial. Several studies, including our original paper dated 1990, suggest an increased incidence in the summer months, but this pattern has not been always confirmed. The present study is concerned with an evaluation of the month of onset of PMR in a large cohort of consecutive PMR patients.
Design and Method. 477 patients with PMR diagnosed according to Bird's criteria, visited between 1990 and 2014, were studied. Of them, 83 (17.4%) were excluded because they could not precisely remember the month of onset of PMR, or another diagnosis emerged at follow-up (median time of 13.8 months; range 1-250 months). 394 patients (251 women, median age 73 yrs, range 47-92 yrs) were analyzed. Clinical features at disease presentation included involvement of: the shoulder girdle; the pelvic girdle; the column; two or more of the previous locations; with giant cell arteritis (GCA); or with acute onset, defined as completion of full symptoms and signs in less than 72h. PMR outcome was evaluated by considering: duration of follow-up; appearance of peripheral arthritis; appearance of GCA; number of exacerbations/ relapses; cumulative dosage of GC; use of methotrexate (MTX); and death.
Results. The month with the highest incidence of PMR was April with 41 (10.6%) cases and that with the lowest incidence was October with 22 (5.7%) patients. There were no monthly or seasonal differences. Demographic and clinical features did not vary according to the month of onset. By contrast, patients with PMR and concomitant GCA had more frequently a presentation during the autumn (14/28 or 50% vs 71/363 or 19.6%; p=0.003). The month of onset did not predict any of the considered outcomes.
Conclusions. Our results confirm a seasonality of onset of PMR, at least in the subset with concomitant GCA at the onset, and support the need of investigating the inciting event at play.

Keywords: polymyalgia rheumatica, giant cell arteritis, season.

OC4:6

ASSESMENT OF ORGAN DAMAGE ACCORDING TO IMACS (INTERNATIONAL MYOSITIS ASSESMENT AND CLINICAL STUDIES) MYOSITIS DAMAGE INDEX IN 92 PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOSITIS

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Objective. Long-term organ damage caused by idiopathic inflammatory myopathies (IIM) and risk factors associated with organ damage have been understudied. In this study we aimed to evaluate the long term organ damage and risk factors, associated with these prospectively in IIM patients.
Design and Method. IIM patients (n=110) who has been followed up for at least six month by our clinic and fulfilling Bohan and Peter criteria were recruited. Demographic data, clinical and serological features, treatment and final clinical status was recorded. IMACS Myositis Damage Index (MDI) was determined twice in 92 patients (71% female) at the time of diagnosis from the records and at last clinical visit prospectively.
Results. Mean age of patients during the diagnosis was 46±14.7. Out of 92 patients 69% had dermatomyositis, 23% polymyositis, 8% necrotizing autoimmune myopathy and inclusion body myositis. Mean follow up was 82 months. Frequencies of dysphagia, respiratory muscle involvement and interstitial lung disease were 29; 5; 34% respectively. Twenty-one percent of the patients had associated malignancy. The mean daily prednisolone dosage and total amount was 7.5 mg/day and 9000 mgs. Mortality was 13%. Initial mean MDI at the time of diagnosis was 1.6±3.0 (range, 0-14) and the last MDI score recorded was 6.1±4.7 (range, 0-21). After the last assessment the proportion of patients without damage was 8%. The last MDI score was significantly higher than the first MDI score (p<0.001). The last MDI in females and patients with calcinosis were significantly high (p=0.002; p=0.007). The last MDI scores and disease duration were weakly correlated (r=0.35 p=0.001). A moderately significant correlation was found between the last MDI score, the duration of glucocorticoid use and the total dose used (r=0.48;r=0.45 p<0.001).
Conclusions. Our long-term follow up data showed that persistent organ damage assessed by MDI and mortality were high in patients with IIM and over half of patients developed severe damage. Organ damage was detected in some patients at presentation and MDI scores were significantly increased during the follow up. MDI scores were found high in females and in patients with calcinosis. There were significant correlations between disease duration, the duration of glucocorticoid use, the total dose used and MDI scores. Current treatments and strategies have been insufficient at improving the prognosis of patients with IIM and new treatment strategies and drugs are needed.

Keywords: myositis, damage, risk factors.

06 – Pregnancy in RMDs: what the patients would like to know

PS1:1

PREGNANCY "YES" IN RHEUMATIC DISEASES: WHAT PATIENTS WOULD YOU LIKE TO KNOW

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The approach to pregnancy in rheumatic diseases (RMDs) has greatly changed over the past few decades, ensuring good pregnancy outcomes for the majority of women and allowing a progressively increasing number of them to realize their family plan. Maternal counselling is a key point to ensure optimal timing of pregnancy (remission or stable disease in the previous 6 months), adequate drugs adjustment, complete autoantibodies panel and comorbidities assessment to detect and manage those related with pregnancy morbidity. Prior to advances in therapies and disease management, many RMDs patients were discouraged from having children for multiple reasons, such as concerns that disease flare during pregnancy

Table I. Preconception checklist for the risk stratification of a patient with RMD planning a pregnancy or currently pregnant.

Maternal risk factors	
Disease activity:	patient in remission or stable disease in the last 6-12 months and at conception
Autoantibodies:	anti-Ro/SS-A antibodies and aPL profile
Serological activity:	serum C3/C4, anti-dsDNA titres
Major organ involvement:	cardiac, pulmonary, renal involvement (*e.g.* severe pulmonary hypertension, severe interstitial lung disease, severe renal failure)
Teratogenic drugs:	methotrexate, mycophenolate, cyclophosphamide
Previous pregnancy complications:	abortions, foetal loss, pre-eclampsia/eclampsia, HELLP syndrome, prematurity, IUGR and SGA infants
Maternal comorbidities:	advanced age, arterial hypertension, diabetes, thyroid disease, overweight/obesity, previous thrombosis and thrombotic risk factors
Harmful lifestyle habits:	nicotine, alcohol, and recreational drugs

Legend: aPL, anti-phospholipid antibodies; HELLP Syndrome, Hemolysis, Elevated Liver enzyme levels, Low Platelet count Syndrome; IUGR, intrauterine growth restriction; SGA, small-for-gestational-age.

Table II. Anti-rheumatic drugs and pregnancy.

WITHDRAWN BEFORE CONCEPTION	STOP AT POSITIVE PREGNANCY TEST	COMPATIBLE WITH PREGNANCY	ADJUNCT TREATMENT DURING PREGNANCY
Methotrexate[a]			
Mycophenolate mofetil[a]	selective COX II inhibitors[b]	NSAIDs (avoid after 32w)	Folic acid (*3mths before conception*)
Cyclophosphamide[a]			
Leflunomide[b]	Warfarin/Acenocumarol	Prednisone	Calcium, Vitamin D
Tofacitinib[b]		Methylprednisolone	
Apremilast[b]			
		Hydroxychloroquine	
Abatacept[c]		Chloroquine	
Tocilizumab[c]		Sulfasalazine (2gr/day)	±LDA[d] (*preconceptionally or <16w*)
Rituximab[c]	Mepacrine[b]	Azathioprine	
Belimumab[c]		Ciclosporin	
Ustekinumab[c]		Tacrolimus	
Secukinumab[c]		Colchicine	
		Infliximab(stop 20w)*	
		Adalimumab(stop 20w)*	
		Golimumab (NA)*	± prophylactic/therapeutic LMWH[e]
		Etanercept (stop 30-32w)*	
		Certolizumab**	
		Anakinra*	
		Intravenous immunoglobulin	

Legend: NSAIDs, non-steroidal anti-inflammatory drugs; w, weeks; NA, not available; mths, months; LDA, low-dose aspirin; LMWH, low molecular weight heparin.
[a] teratogenic;
[b] avoid until further evidence is available;
[c] limited documentation on safe use in pregnancy and should be replaced before conception by other medication.
[d] if risk of preeclampsia, e.g. patients with lupus nephritis or aPL positive patients.
[e] In Anti-phospholipid syndrome, according to clinical manifestations of Anti-phospholipid syndrome or aPL risk profile.
*if maternal disease activity cannot be controlled with different drugs.
**demonstrated lack of transplacental passage (possible use throughout pregnancy if required by maternal disease activity).

could affect their health or their baby's health and that disease-related disability might have an impact on their ability to care for a child. Recent data from national health care databases has showed an increase in the numbers of children born to mothers with inflammatory arthritis, reflecting the development of better and safer therapeutic strategies. In fact, high disease activity has been recognized as one of the most detrimental prognostic factors for adverse pregnancy outcome. Thefore, the use of drugs for achieving remission prior to and during pregnancy is considered as beneficial not only for the mother but also for fetal wellbeing. Nowadays, a large proportion of medications are compatible with pregnancy without causing any evident harm to the children. Moreover, adjuntive therapies can improve maternal and foetal oucomes in specific situations, such as patients at risk of preeclampsia or thrombosis. As stated by the recent EULAR recomendations, women at higher risk of pre-eclampsia, like those with lupus nephritis or anti-phospholipid antibodies (aPL) will benefit from low-dose of aspirin (LDA). In patients with a definitive diagnosis of obstetric Anti-phospholipid syndrome (APS) or aPL-positive women with moderate to high risk of maternal and fetal complications, LDA and prophylactic heparin should be associated. RMDs *per se* do not seem to decrease fertility. However, active disease and the use of some drugs may negatively impact on fertility. Alkylating agents such as cyclophosphamide may cause menstrual irregularities and premature ovarian failure, which is age-and dosage dependent. Non-selective and selective cyclooxygenase inhibitors can induce the luteinised unruptured follicle syndrome in a dose-dependent and menstrual cycle-dependent manner. Women facing the prospect of gonadotoxic therapies or with problems of infertility could have the opportunity to discuss their options with a reproductive endocrinologist. Assisted reproductive technologies are generally safe in women affected with RMDs if the timing of the procedure has been planned with the rheumatologist in order to add adequate pharmacological prophylaxis. Pregnancy is an exciting time for RMDs patients, but it can raise a lot of questions and concerns about how the pregnancy can influence the disease or how the disease and drugs will affect them and their babies. It's important to identify any risk for the individual patient and her child in regard to pregnancy. Preconception counselling, stable disease control, use of safe medications are the requirement for good outcomes. The rheumatologist plays an important role in helping patients to take informed health choices during pregnancy and integrating the approach of the Obstetrician.

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PS1:2

PREGNANCY "NO" IN RHEUMATIC DISEASES: WHAT PATIENTS WOULD YOU LIKE TO KNOW

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Rheumatic Diseases (RMDs) mainly affect women and their onset frequently occurs during reproductive years, therefore the discussion of reproduction issues with patients is a crucial point. Concerns include the effect of pregnancy on maternal disease, the impact of disease activity on foetal health and the safety of medications during pregnancy.
Some conditions may be a serious threat to maternal and foetal/neonatal health. Patients with severe major organ involvement (pulmonary, cardiac, renal, central nervous system) should be discouraged from pregnancy because of increased morbidity and mortality. Caution should be used in women with previous hemolysis, elevated liver enzymes, and low platelet count occurring in association with preeclampsia and/or HELLP syndrome and recent arterial thrombosis.
In patients with active disease or with a new-onset RMD, the pregnancy should be postponed until remission or stable disease is achieved and has persisted for at least 6 months. At an early stage of disease, the pattern of disease severity is not yet apparent and frequent adjustment of therapy could be necessary. This strategy, however, must be balanced against the disadvantages that advancing maternal age can exert on fertility and pregnancy outcome.
Drugs like methotrexate, mycophenolate mofetil, and cyclophosphamide are teratogenic, so no prescription should be given without first excluding pregnancy and ensuring comprehensive information on safe and effective contraception according to the individual risk. Teratogenic drugs should be stopped before conception and replaced by other medication compatible with pregnancy.
Risk assessment for possible maternal or foetal risks during a future pregnancy is essential for counseling an individual patient, adjusting therapy and patient-tailored monitoring plan before and during pregnancy. A clinical and laboratory work-up should be performed and potential risk factors for pregnancy complications should be identified: disease-related risk factors, particularly disease activity and anti-Ro/SSA and anti-La/SSB and antiphospholipid antibodies (aPLs), and general risk factors (advanced age, arterial hypertension, diabetes, overweight/obesity, tobacco/alcohol/recreational drugs use).
Risk stratification and actions to minimize it are likely to be the key points for the significant improvement of the pregnancy outcomes observed in the last decades in RMDs. However, some conditions and teratogenic drugs may seriously threaten maternal and fetal/neonatal health. The preconception counselling is crucial to identify all the potential adverse risk factors to reduce and manage them. A multidisciplinary medical team (rheumatologist, gynecologist, neonatologist) has to offer the most complete and comprehensive information and the best strategies to ensure a good pregnancy plan and to guide the choice of the patient and her family.

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3. ANDREOLI L *et al*.: *Ann Rheum Dis* 2017; 76: 476-85.

Table I. Controindications to pregnancy in women with rheumatic diseases.

Reasons to *postpone* pregnancy
- Patients with active disease during the last 6 months;
- Patients with recent-onset disease;
- Treatment with teratogenic drugs.

Reasons to *controindicate* pregnancy
- Patients with severe organ involvement: severe renal, pulmonary, cardiac, central nervous system impairment or any severe organ damage.

07 – Sun, vitamin D and rheumatic diseases

L5:1

SUN, VITAMIN D AND RHEUMATIC DISEASES

Maurizio Cutolo

Recently, vitamin D is receiving an increased attention for its involvement in reducing risk for several chronic diseases including many cancers, infectious diseases, type-1 diabetes and in particular autoimmune rheumatic diseases.
The final active metabolite of vit D (1,25(OH)D3) is considered a steroid hormone for its origin from cholesterol (D-hormone), and therefore like glucocorticoids may exert immunomodulatory activities (GC).
Ultraviolet (UV) radiations produced by the sun are the major source of vit D by inducing the synthesis of the precursors at the level of the skin. Several physiopathological investigations confirm that severe deficiency of vit D, in genetically predisposed subjects, can impair self tolerance and immune responses by compromising the regulation of dendritic cells, regulatory T-lymphocytes (Tregs), Th1 cells and B cell function. Cross-sectional studies have shown that deficient serum levels of vit D (25(OH)D) (<20 ng/mL) are present in a significant percentage, not only in patients with autoimmune diseases such as type-1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), but also in healthy subjects and especially in winter/spring time.
Furthermore, the presence of severe serum 25(OH)D deficiency (<10ng/mL) seems also involved in the generation of symptoms that characterize patients with rheumatic diseases, (*i.e*. musculoskeletal pain in RA), and supplementation seems to induce improvements. The suggested role for low serum 25(OH)D as risk factor in autoimmunity seems clearly supported also by some recent investigations showing that even antinuclear antibodies (ANA)-positive healthy controls are significantly more likely to be deficient in vit D serum levels than ANA-negative healthy controls. On the other hands, vitamin D supplementation was found associated in a recent survey with a significant increase of Tregs frequency in apparently healthy individuals.
Furthermore, a significantly higher frequence of autoantibodies (anti-Jo-1) was also confirmed in idiopatic inflammatoy myopathy (IIM) patients that had significantly lower median serum 25(OH)D levels compared to controls. In couple with the finding that vit D deficiency is associated in SLE patients with certain immune abnormalities and significantly correlates in a negative manner with clinical SLE activity and anti-dsDNA titer, it is now strongly suggested that vit D deficiency plays an important role in enhancing autoantibody production and at least B cell autoimmunity.
In an interventional study evaluating the immunological effects of vit D supplementation in 20 SLE patients with hypovitaminosis D, a decrease of memory B cells and anti-DNA antibodies together with a preferential increase of naive $CD4^+$ T cells, an increase of regulatory T cells and a decrease of effector Th1 and Th17 cells has been reported. As matter of fact, a novel role for low vit D as risk factor and/or modifyer of autoimmune response is now suggested In fact, it is proposed that deprivation of solar light or low serum 25(OH)D at higher latitudes, facilitates the development of autoimmune diseases by aggravating the $CD8^+$ T-cell deficiency, thereby further impairing control of EBV and permitting clonal expansion of autoreactive B cells EBV-infected.
The result is that at least in B cell immune diseases, the vit D deficiency plays a true role as risk factor by enhancing other concomitant factors.

08 – The impact of nutrition and lifestyle on RMDS

ES1:1

NUTRITION AND RHEUMATIC DISEASE: ARE WE REALLY WHAT WE EAT?

Elena Philippou PhD

Purpose. To explore which foods and/or dietary patterns are associated with the risk of rheumatic and musculoskeletal diseases (RMDs).
Methods. Research studies associating diet and RMDs were identified through MEDLINE.
Results. A number of dietary factors might act as environmental triggers in disease development. Overall, a 'Western' type diet rich in energy intake, total and saturated fat, an unbalanced ratio of n-3 to n-6 fatty acids, high in sugar and low in fiber and antioxidants might increase the risk of RMDs both directly through increasing inflammation (Minihane et al. 2015) and indirectly through increasing insulin resistance, obesity and associated co-morbidities, with obesity being a known risk factor for RD (Qin *et al*. 2015).
High consumption of foods characteristic of the 'Western-type' diet such as red meat, meat and meat products combined, or total protein have been shown to increase the risk of inflammatory polyarthritis suggesting a role of advanced glycation end products (AGEs) (Pattison *et al*. 2004). This is supported by findings of regular consumption of sugar-sweetened soda, but not diet soda, being associated with an increased risk of seropositive rheumatoid arthritis (RA) in women (Hu *et al*. 2014), and of high-fructose corn-syrup sweetened soft drinks, fruit drinks and apple juice being associated with arthritis in young US adults (DeChristopher *et al*. 2016). It is hypothesized that regular consumption of excess free fructose and HFCS contributes to fructose reactivity in the gastrointestinal tract and intestinal in situ formation of enFruAGEs, which once absorbed, travel beyond the intestinal boundaries to other tissues and promote inflammation (DeChristopher *et al*. 2016). Individual biomarkers of antioxidant intake have also been previously investigated in relation to RA with some evidence that low serum levels of selenium and alpha tocopherol (Knekt *et al*. 2000) and beta carotene (Comstock *et al*. 1997) are associated with an increased disease risk. Interestingly, a meta-analysis also suggests that coffee consumption of ≥ four cups per day is associated with an elevated risk of seropositive RA but not seronegative RA (Lee *et al*. 2014). However, the results should be interpreted with caution due to other potential confounders. The same meta-analysis found no association between tea consumption and risk of RA (Lee *et al*. 2014).
On the contrary, consumption of long-chain omega-3 polyunsaturated fatty acids, derived from fish and fish oil, is associated with a reduced risk of RA (Di *et al*. 2014) probably due to their anti-inflammatory properties. The Mediterranean diet (MD), rich in plant-based foods such as wholegrains, legumes, fruit, vegetables, extra-virgin olive oil and low in red meat consumption, might have the potential to reduce the risk of RA. It has been shown that greater adherence to the MD is associated with lower concentrations of inflammatory biomarkers (Fung *et al*. 2005), while daily consumption of monounsaturated fatty acids from olive oil is thought to be the key factor in suppressing RA disease activity (Matsumoto *et al*. 2017).
Conclusions. Based on current research evidence, it is suggested that adherence to the MD with an increased consumption of fatty fish, reduced consumption of sugar-sweetened drinks and maintenance of a normal body weight, contributes to reducing the risk of RA. Further research on RA susceptibility will allow more specific dietary recommendations.

ES1:2

THE SUN AND RHEUMATIC DISEASES: FRIEND OR FOE?

Maurizio Cutolo

Generally we must underline that the sunlight is a natural medicine.
Why is a friend?
- Sunlight lowers cholesterol
- Sunlight can cure depression
- Regular sunlight exposure increases the growth and height of children
- Sunlight prevent cancer
- The sun's light kills bacteria
- Sunlight has a beneficial effect on skin disorders
- Sunlight builds the immune system and protect from autoimmune diseases
- Sunlight protect from some rheumatic diseases including osteoporosis

How the sun protects our health and from rheumatic diseases?
In order to well understand how the sun exert his before mentioned beneficial effects, we should consider that all the functions are related to the sun Ultra Violet (UV) radiations that are mediated in the human body through the synthesis of the D hormone (so called vitamin D). As matter of fact, cross-sectional studies have shown that deficient serum levels of vit D (25(OH)D) (<20 ng/mL) are present in a significant percentage, not only in patients with autoimmune diseases such as type-1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), but also in healthy subjects and especially in winter/spring time. Therefore, winter time is a dangerous time for infections, high cholesterol, skin diseases including psoriasis, and of course osteoporosis.
Furthermore, the presence of severe serum 25(OH)D deficiency (<10ng/mL) seems also involved in the generation of the symptoms that characterize patients with rheumatic diseases, (i.e. musculoskeletal pain in RA), and supplementation seems to induce improvements.
The suggested role for low serum 25(OH)D as risk factor in autoimmunity seems clearly supported also by some recent investigations showing that even antinuclear antibodies (ANA)-positive healthy controls are significantly more likely to be deficient in vit D serum levels than ANA-negative healthy controls. On the other hands, vitamin D supplementation was found associated in a recent survey with a significant increase of Tregs frequency in apparently healthy individuals. In couple with the finding that vit D deficiency is associated in SLE patients with certain immune abnormalities and significantly correlates in a negative manner with clinical SLE activity and anti-dsDNA titer, it is now strongly suggested that vit D deficiency plays an important role in enhancing autoantibody production and at least B cell autoimmunity.
Interestingly, since only 20% of the daily need of vitamin D can be obtained by the diet (80% from UV), vitamin D supplementation is a more accepted practice with important control (as steroid hormone) of both innate and adaptive immune response, especially with increasing recognition that vitamin D insufficiency/deficiency is a frequent observation in RA. Patient reported outcomes (PRO) in RA seem to help in detecting/predicting by clinical symptoms, the effects of the epidemic deficiency of vitamin D/ D hormone especially during winter time. To be noted that when atmospheric conditions are ideal and skies are clear, 30 minutes of whole-body exposure of pale skin to sunlight without clothing or sunscreen can result in the synthesis of between 10,000 and 20,000 IU of vitamin D. These quantities of vitamin D are large, and therefore capable of supplying the body's full needs.
In conclusion, the sun in rheumatic diseases is just a friend and never a foe.
Recently, vitamin D is receiving an increased attention for its involvement in reducing risk for several chronic diseases including many cancers, infectious diseases, type-1 diabetes and in particular autoimmune rheumatic diseases. The final active metabolite of vit D (1,25(OH)D3) is considered a steroid hormone for its origin from cholesterol (D-hormone), and therefore like glucocorticoids may exert immunomodulatory activities (GC). Ultraviolet (UV) radiations produced by the sun are the major source of vit D by inducing the synthesis of the precursors at the level of the skin. Several physiopathological investigations confirm that severe deficiency of vit D, in genetically predisposed subjects, can impair self tolerance and immune responses by compromising the regulation of dendritic cells, regulatory T-lymphocytes (Tregs), Th1 cells and B cell function. Cross-sectional studies have shown that deficient serum levels of vit D (25(OH) D) (<20 ng/mL) are present in a significant percentage, not only in patients with autoimmune diseases such as type-1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), but also in healthy subjects and especially in winter/spring time. Furthermore, the presence of severe serum 25(OH)D deficiency (<10ng/mL) seems also involved in the generation of symptoms that characterize patients with rheumatic diseases, (*i.e.* muskuloskeletal pain in RA), and supplementation seems to induce improvements. The suggested role for low serum 25(OH)D as risk factor in autoimmunity seems clearly supported also by some recent investigations showing that even antinuclear antibodies (ANA)-positive healthy controls are significantly more likely to be deficient in vit D serum levels than ANA-negative healthy controls. On the other hands, vitamin D supplementation was found associated in a recent survey with a significant increase of Tregs frequency in apparently healthy individuals. Furthermore, a significantly higher frequence of autoantibodies (anti-Jo-1) was also confirmed in idiopatic inflammatoy myopathy (IIM) patients that had significantly lower median serum 25(OH)D levels compared to controls. In couple with the finding that vit D deficiency is associated in SLE patients with certain immune abnormalities and significantly correlates in a negative manner with clinical SLE activity and anti-dsDNA titer, it is now strongly suggested that vit D deficiency plays an important role in enhancing autoantibody production and at least B cell autoimmunity. In an interventional study evaluating the immunological effects of vit D supplementation in 20 SLE patients with hypovitaminosis D, a decrease of memory B cells and anti-DNA antibodies together with a preferential increase of naive $CD4^+$ T cells, an increase of regulatory T cells and a decrease of effector Th1 and Th17 cells has been reported. As matter of fact, a novel role for low vit D as risk factor and/or modifier of autoimmune response is now suggested In fact, it is proposed that deprivation of solar light or low serum 25(OH) D at higher latitudes, facilitates the development of autoimmune diseases by aggravating the $CD8^+$ T-cell deficiency, thereby further impairing control of EBV and permitting clonal expansion of autoreactive B cells EBV-infected. The result is that at least in B cell immune diseases, the vit D deficiency play a true role as risk factor by enhancing other concomitant factors.

ES1:3

IMPACT OF DIET IN ESTABLISHED RHEUMATIC DISEASES: WHAT DO WE KNOW? HOW DOES IT WORK?

Claire I. Daïen

Purpose. Many patients believe diet might help controlling their rheumatic diseases. Although it is a very fashionable topic, scientific data is limited and rheumatologists often have difficulties answering their patients' questions.
Methods. An evidence-based medicine approach will be used.
Results. The current state of knowledge on the impact of micronutrients (vitamins, salt, spices, etc.), macronutrients (carbohydrates, lipids, fibers, etc.), exclusion diets (lactose, gluten, fasting, etc.) and weight loss on rheumatic diseases will be presented. Limits and biases of nutritional studies will be discussed. Basic knowledge on how diet can influence immune cells will be presented.
Conclusion. Further high-quality studies are needed. However, some practical dietary advice can be given to patients with rheumatic diseases.

09 – Fostering physical activity together with correct nutrition

L6:1

FOSTERING PHYSICAL ACTIVITY TOGETHER WITH CORRECT NUTRITION: A SUCCESSFUL APPROACH BUT RARELY RESPECTED IN RMDs

George D. Kitas

RMDs are characterised by pain, stiffness and limited mobility; occasionally significant changes to family, employment and social roles; and significant co-morbidities, including cardiovascular disease. People with RMDs engage in little physical activity and may have limited ability and opportunity to follow a healthy diet. The possible barriers to sufficient physical activity engagement and a healthy lifestyle have been investigated and could be addressed to a certain extent by successful medicinal therapy but also psychoeducational interventions. There is a lot of evidence to demonstrate that reduced sedentary behaviour, increased physical activity and structured exercise provide very significant benefits in terms of symptom control, functional ability, quality of life and overall well-being as well as cardiovascular risk reduction in people with RMDs. Several dietary interventions have been evaluated in many studies of variable quality with mixed results – there is however a consistent stream of evidence that healthy dietary habits, such as those of the Mediterranean diet, may provide benefits to people with RMDs. It should not be forgotten that the overall underlying principal is this of an overall healthy lifestyle, as in many traditional Mediterranean countries until recently, including physical activity engagement, socialising, sufficient rest and healthy eating. Ways by which people with RMDs (as well as the general population) could be enabled and empowered to follow again such a lifestyle need to be investigated in a multidisciplinary fashion.

10 – FIFTH SESSION: From Raynaud's phenomenon up to Systemic Sclerosis

S5:1

SYSTEMIC SCLEROSIS: EPIDEMIOLOGY, NUTRITIONAL ASPECTS AND ENVIRONMENTAL FACTORS

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Objective: Several registries (*e.g.* EUSTAR, DNSS, and others) have shown that although SSc can still be regarded a rare disease, more than 20.000 patients are accessible for data acquistion and evaluation. The results of these registries show that both the limited and diffuse form inherit involvement of the skin and the different organs, although to a different extent. They also show that individuals from all continents can be affected, generally independent of overt environmental factors or factors that have been thought to be key environmental triggers. On the other hand, more recently discovered environmental factors such as epigenetic modifications can significantly influence and alter the course of the disease or aggravate the outcome, e.g. by smoking. One of the most interesting aspects, however, is the growing interest in the microbiome driving parts of the pathopysiology, a component which might even be modified by diet.
Design and Method.
Results.
Conclusions.

Keywords: systemic sclerosis, epidemiology, environmetal factors.

S5:2

SYSTEMIC SCLEROSIS: EARLY DISEASE CLINICAL FEATURES AND DIAGNOSTIC TOOLS

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Systemic sclerosis (SSc) is a chronic autoimmune disease, characterized by a high level of clinical heterogeneity and associated with a high morbidity and mortality. SSc is easy to diagnose in the advanced phase, when it is evolved to skin fibrosis and significant internal organ damage while it is very difficult in the early phase characterized by aspecific symptoms/signs as Raynaud's phenomenon (RP) and puffy fingers (PF) also presents in several other connective tissue disordes, However RP and PF are considered as "red flags" to suspect the presence of the SSc, and when are presents, frequently abnormal nailfold capillaries and specific autoantibodies can be also found. In early stages, patients may also have digital ulcers as well as. internal organ involvement as inverted mitral E/A ratio (*i.e.* diastolic dysfunction as a measure of early cardiac involvement) and/or a transfer factor for carbon monoxide (TLCO)<80% of the predictive value (*i.e.* early lung interstitial/vascular involvement) and/or basal low oesophageal sphincter pressure <15mmHg (i.e. early oesophageal involvement). An early diagnosis is still the weak point but the crucial element in the fight against this disease. Unfortunately internal organ involvement is often asymtpomatc in earliest phases, for this reason new sensitive instrumental tools as heart and lung MRI, lung ultrasound or biomarkers, as specific antibodies, chemockines, interleukines. may be useful in the management of SSc patients. The new highly specific and sensitive 2013 ACR/EULAR classification criteria add emphasis to the vasculopathic manifestations (pulmonary arterial hypertension, telangiectasia, abnormal nailfold capillaries), encouraging a more aggressive therapeutic strategy aimed at the earliest vascular manifestation. However, to limit the risk of an overtreatment of patients who are not destined to evolve into established disease, the only feasible clinical strategy in *thr early phase of disease* remains a close follow up and an aggressive treatment of early internal organ involvement as they appear-- as reliable predictive biomarkers for disease evolution are, unfortunately, missing.

S5:3

MANAGEMENT OF SYSTEMIC SCLEROSIS: FROM GUIDELINES UP TO THE LAST TREATMENT ISSUES

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Objective. Although systemic sclerosis remains challenging there has been significant recent progress in management that is underpinned by completion of clinical trials and observational studies that confirm benefit from treatments for specific complications of the disease such as digital ulcers and pulmonary arterial hypertension.
Design and Method. Published evidence will be presented that supports benefit from licensed treatments for vascular complications of systemic sclerosis will be presented. In addition the benefit of immunosuppression is now clearly shown by studies of agents such as cyclophosphamide and also be the dramatic benefit from haematopoietic stem cell transplantation after high intensity immunosuppression.
Results. The EULAR/EUSTAR recommendation for management of systemic sclerosis were updated recently and a BSR/BHPR treatment guideline that is accredited by the National Institute of Health and Care Excellence (NICE) in UK has also been developed. These approaches support harmonised and evidence based practice that will provide the platform for further clinical progress. A number of innovative clinical trails for systemic sclerosis are underway and it is hoped that these will help move towards definitive targeted therapy that may benefit systemic sclerosis and other forms of fibrosis.
Conclusions. Current approaches to managing systemic sclerosis will be reviewed and emerging treatments will be discussed to provide a framework for optimal management of this condition that has high associated morbidity and mortality.

Keywords: guidelines, scleroderma, fibrosis.

S5:4

MANAGEMENT: NON-PHARMACOLOGICAL ASPECTS AND UNMET NEEDS

O. Distler, Zurich

Purpose. With the advancements in targeted therapies in systemic sclerosis, focus in the coming years will shift to further unmet needs including non-pharmacological interventions, combination therapies, precision medicine and detection of early organ and disease development.
Methods. This review talk is based on systematic literature review and nominal group expert opinion.
Results. Little evidence exists for non-pharmacological interventions. High-quality evidence is limited to oral health interventions and orofacial exercises, multidisciplinary team-care programs to improve mouth opening and hand grip strength, and to manual lymph drainage to improve hand function. Similarly, combination therapies are limited to observational studies, but currently ongoing large scale RCTs allow immunosuppressive background therapy, and some of the targeted therapies such as multi-tyrosine-kinase inhibitors are combination therapies per se from their mode of action. Precision medicine is a major goal for the upcoming years and significant advances have been made using large-scale molecular screening and targeted diagnostic approaches. Finally, early detection of overall disease and organ involvement is some of the most significant steps forward in SSc from the last years and examples include early detection of PAH (DETECT), ILD (SPAR), and overall disease (VEDOSS).
Conclusion. Early referral to SSc centers is getting more and more important, as our possibilities for early detection of overall disease and organ involvements, early intervention with targeted therapies alone or in combination, based on individualized diagnostic approaches and personalized treatment decisions are increasing rapidly.

11 – From Raynaud's phenomenon up to Systemic Sclerosis

OC5:1

ASSOCIATION OF INTERLEUKIN-17 AND INTERLEUKIN-23 MRNA AND PROTEIN EXPRESSION PROFILES WITH CLINICAL PRESENTATION IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective. Growing evidence suggests that T-cell proliferation and cytokine secretion play an important role in the pathogenesis of systemic sclerosis (SSc). In this study we evaluated interleukin-17 (IL-17) and interleukin-23 (IL-23) mRNA and protein expression profiles and investigated their association with organ involvement in SSc patients.
Design and Method. Study included 63 SSc patients and 13 healthy controls. We analyzed IL-17A, IL-17F and IL-23 mRNA expression in peripheral blood mononuclear cells (PBMNCs) by quantitive Real-Time Polymerase Chain Reaction (qRT-PCR). Enzyme-Linked Immunosorbent Assay (ELISA) was used for analysis of IL-17 and IL-23 serum protein levels.
Results. IL-17A mRNA level was increased in all patients with SSc and significantly increased in patients with disease duration of 5 to 10 years and >15 years (4.7 vs 1.2 and 6.1 vs. 1.2, $p<0.05$, respectively) compared to controls. In patients with disease duration <5 years, IL-17F mRNA and IL-23 mRNA were decreased, compared to controls (0.63 vs. 1.2 and 0.73 vs. 1.1, $p<0.05$). IL-17 and IL-23 serum protein concentrations were higher in patients with interstitial lung involvement (ILD) compared to SSc patients without ILD ($p<0.05$). IL-23 serum protein level was positively associated with total GIT score (r 0.35, $p<0.05$).
Conclusions. Our results showed a correlation between disease duration and IL-17A, IL-17F and IL-23 mRNA levels in SSc. IL-17 protein overproduction in SSc patients may be associated with ILD, while IL-23 level correlate with gastrointestinal impairment.

Keywords: systemic sclerosis, interleukin-17, interleukin-23.

OC5:2

VITAMIN D DEFICIENCY IN SYSTEMIC SCLEROSIS: CORRELATIONS WITH MULTIPLE CLINICAL PARAMETERS, SEASONAL VARIATIONS AND TREATMENT EFFECTIVENESS IN EUROPEAN SSC PATIENTS

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Objective. In SSc patients, low 25-hydroxyvitamin D (25(OH)D) serum concentrations have been shown (1). Primary aim of the study was to evaluate correlations of 25(OH)D serum levels with multiple clinical parameters and with seasonality, in patients with systemic sclerosis (SSc). Secondary aim was the evaluation of the effects of replacement therapy.
Design and Method. 154 SSc patients were recruited. 25(OH)D serum concentrations were evaluated using LIAISON 25-OH (Diasorin, Italy). Medsger's disease severity scale (DSS), peripheral video capillaroscopy (VCP) and all instrumental examinations covered by the international guidelines have been evaluated (2). Assumption of any medication, including oral cholecalciferol, was considered in the analysis. Non-parametric tests were used for statistical analysis.
Results. The 25(OH)D mean serum concentration was 18.7±9 ng/ml (<20 classified as a deficiency). Statistically significant correlation was found with presence/absence of bi-basal fibrotic abnormalities at lung CT scan (16.1±8 ng/ml and 20±10 ng/ml respectively, $p=0.04$).
DSS parameters correlating with serum concentrations of 25(OH)D were: peripheral vascular system ($p=0.03$), kidney ($p=0.02$), gastrointestinal tract ($p=0.05$). No correlation was observed with the incidence of digital ulcers, which was instead related to capillaroscopic patterns ($p<0.0001$). Significant differences in 25(OH)D serum concentrations were reported in different seasons (winter: 14.6±7.8 ng/ml, spring: 17.2±7.9 ng/ml, summer: 21.43±10 ng/ml, autumn: 20.2±10 ng/ml, $p=0.032$). Interestingly, no effect of oral supplementation (cholecalciferol 1000 UI per day for at least 6 months) was observed on serum concentrations of 25(OH)D (18.8±10 ng/ml in treated patients and 18.7±9 ng/ml in untreated patients, $p=0.81$).
Conclusions. 25(OH)D deficiency resulted correlated with advanced lung involvement and with the following DSS scale parameters according to Medsger: peripheral vascular system, kidney, gastrointestinal tract. 25(OH)D serum concentrations resulted correlated with seasonality and supplementation with oral cholecalciferol was not effective in increasing serum concentrations of 25(OH)D. Therefore, for a successful therapy, evaluation of high doses of cholecalciferol or ultraviolet exposure would be needed (3).

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Keywords: vitamin D, systemic sclerosis, cholecalciferol treatment.

OC5:3

TYPE I INTERFERON INDUCED GENE EXPRESSION IN THE PERIPHERAL BLOOD OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective. Increasing data suggests a key role of innate immunity in systemic autoimmune diseases, including Systemic Sclerosis (SSc). Type I Interferon (IFN) pathway represents a therapeutic target in SSc currently being tested in clinical trials. However, to date, no distinct SSc phenotype has been associated with high type I IFN levels. On the other hand, in vitro experiments using plasmacytoid dendritic cells from patients with SSc suggest an interplay between platelet factor 4 (PF4/CXCL4), a potential biomarker in SSc, and TLR-induced IFNa expression. Our study tests the hypothesis that type I IFN-induced gene expression in the peripheral blood may associate with particular clinical and laboratory features, including plasma CXCL4 levels, in patients with SSc.

Design and Method. Ninety-four SSc patients (61 limited – 33 diffuse, 87 women, mean age ± SD: 54±14 years, disease duration: 0.5-27 years) and 20 healthy controls (HC) were examined. RNA was isolated from peripheral whole blood samples following erythrocyte lysis. cDNA was synthesized, the expression of 3 genes preferentially induced by type I IFN (IFIT1, MX1, IFI44) was quantified by qPCR and individual type I IFN scores were calculated; scores were considered high when exceeding the mean+3SD of the corresponding HC scores. Plasma CXCL4 levels were determined by ELISA.
Results. A high type I IFN score (>8) was found in 31/94 (33.0%) patients with SSc, ranging from 8.4 to 145, compared with 0/20 HC (p=0.002). High type I IFN scores associated with higher ESR (p=0.03) and lower DLCO levels (p=0.01) among SSc patients (Mann-Whitney U test). Other disease variables, *i.e.* extent of skin involvement or auto-antibodies, were not associated with high type I IFN scores. Individual type I IFN scores positively correlated with the corresponding CXCL4 levels in available plasma samples (Spearman's rho: 0.53, n=20, p=0.02), as well as with follow-up IFN scores in 10 randomly selected patients (Spearman's rho: 0.71, p=0.02).
Conclusions. A high type I IFN score was detected in one third of patients with SSc in association with higher ESR, reduced DLCO levels and higher CXCL4 plasma levels. Further prospective data are required to establish the role of type I IFN as a prognostic biomarker in SSc.

Keywords: systemic sclerosis, type I interferon, CXCL4.

OC5:4

CORRELATIONS BETWEEN SKIN BLOOD PERFUSION AND CHOROIDAL THICKNESS IN SYSTEMIC SCLEROSIS PATIENTS BEFORE AND AFTER A SHORT TIME TREATMENT WITH PROSTACYCLIN ANALOGUE

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Objective. The aim of this study was to evaluate possible correlation between skin blood perfusion (BP), measured by laser speckled contrast analysis (LASCA), and choroid thickness (CT), measured by optical coherence tomography (OCT), in SSc patients, before and after iloprost treatment.
Design and Method. Twelve SSc patients according to ACR/EULAR 2013 criteria (mean age 58±13 years, mean disease duration 5±3 years) underwent BP evaluation by LASCA and ophthalmologic evaluation by OCT, before (T0) and after eight hours of continuous prostacyclin analogue (iloprost) i.v. infusion (0.5 ng/kg/min) (T8). BP was assessed at the level of fingertips, periungueal, whole face, perioral and periorbital area, and the average BP measured as perfusion units (PU) (1). OCT images were recorded by 3D-2000 OCT (Topcon, Japan), and CT area measurements were manually performed using image J software (2).
Results. BP was found significantly increased after iloprost therapy in all examined skin areas (fingertips 96 vs 119; periungueal 101 vs 120; whole face 178 vs 184, perioral 119 vs 126 and periorbital area 191 vs 199, respectively at T0 and T8, p<0.002). No statistically significant variation of CT values was observed after iloprost administration (p=0.7). Statistically significant positive correlations were found between BP and CT, before and after iloprost therapy, at periorbital (T0 r=0.55 p=0.022 and T8 r=0.91 p=0.0002), perioral (T0 r=0.75 p=0.002 and T8 r=0.61 p=0.012), whole face (T0 r=0.49 p=0.04 and T8 r=0.47 p=0.05), fingertips (T0 r=0.69 p=0.004 and T8 r=0.63 p=0.01) and periungueal skin areas (T0 r=0.54 p=0.02 and T8 r=0.50 p=0.04). Patients did not complain any visual/ocular symptom during and after iloprost infusion.
Conclusions. This study demonstrates a correlation between skin BP and CT in SSc patients, but no variation of CT values was observed after short time treatment with prostacyclin analogue. The results further confirm that LASCA may be a tool to monitor BP changes during microvascular targeted treatments.

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Keywords: systemic sclerosis, skin blood perfusion, choroidal thickness.

OC5:5

RELIABILITY OF SIMPLE CAPILLAROSCOPIC DEFINITIONS TO DESCRIBE CAPILLARY MORPHOLOGY IN RHEUMATIC DISEASES

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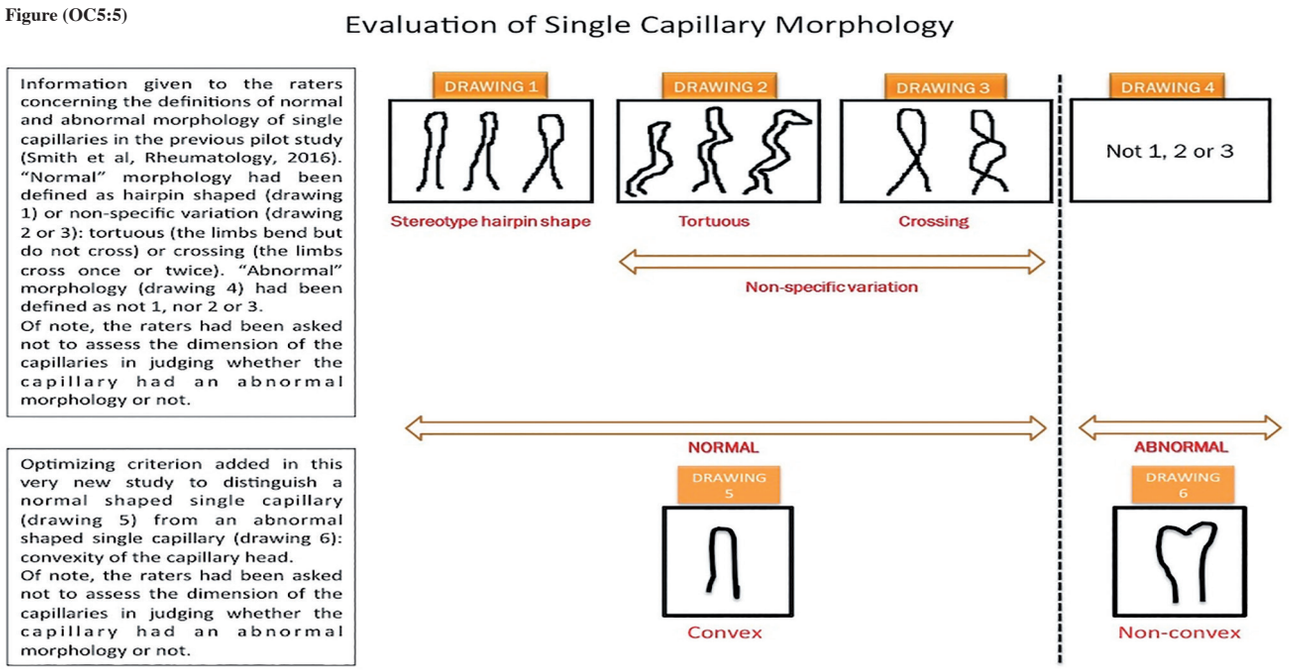
Figure (OC5:5)



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Objective. The EULAR study group on microcirculation in rheumatic diseases has previously proposed simple definitions for interpretation of capillaroscopic morphology of single capillaries, which resulted in moderate reliability. This study has the aim to further optimize these definitions.
Design and Method. To fine-tune the existing definitions (normal – hairpin, tortuous or crossing; abnormal – not hairpin, not tortuous and not crossing), convexity of the capillary head was added as a condition to be evaluated as normal (Figure).
Thirty images with good visibility of single capillaries were presented to the attendees of the seventh EULAR Course on capillaroscopy (Genoa 2016). Attendees (n=119) were asked to categorize themselves into one of the following levels of expertise in capillaroscopy: no experience (novices), n=69; less than 5 years of experience, n=41 and more than 5 years of experience, n=9. Also, 5 independent experts (AH, FI, AS, MC and VS) evaluated the capillaries. Inter-rater agreement was assessed by calculation of the Cohen's kappa between each rater pair of all possible combinations of attendees and the gold standard (GS) and then averaged to provide the Light kappa. In addition, the Cohen's kappa scores between each attendee and the GS were averaged to obtain a mean index of reliability of the attendees to the GS.
Results. The resulting Light kappa based on 30 capillaries was 0.78 for all EULAR course attendees and 0.82 for the 5 independent experts. More specifically, the Light kappa was 0.84 for experienced attendees, 0.78 for moderately experienced attendees and 0.77 for novices. The mean Cohen's kappa coefficient of all attendees to the GS was 0.81 (95% CI: 0.79-0.83). The mean Cohen's kappa between each attendee and the GS was 0.83 (95% CI: 0.78-0.88) for experienced attendees, 0.81 (95% CI: 0.77-0.85) for moderately experienced attendees and 0.80 (95% CI: 0.77-0.83) for novices. The mean Cohen's kappa between each expert in capillaroscopy and the GS was 0.81 (95% CI: 0.71-0.92).
Conclusions. This study showed excellent reliability of optimized simple capillaroscopic definitions for describing morphology of capillaries by rheumatologists with varying levels of expertise.

Keywords: systemic sclerosis, nailfold capillaroscopy, reliability.

OC5:6

MACITENTAN CONTRASTS THE ACTIVATION OF PROFIBROTIC INTRACELLULAR SIGNALING PATHWAYS INDUCED BY ENDOTHELIN-1 IN PRIMARY CULTURES OF SKIN FIBROBLASTS ISOLATED FROM HEALTHY SUBJECTS

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Objective. Myofibroblasts are final key mediators of the fibrotic process in several autoimmune connective tissue diseases, including systemic sclerosis (SSc), where they contribute to the excessive synthesis and deposition of extracellular matrix (ECM) molecules, primarily type I collagen (COL1) and fibronectin (FN) in skin and internal organs. Endothelin-1 (ET-1) plays an important role in SSc, inducing the transition of fibroblasts into profibrotic myofibroblasts and the increase in ECM protein synthesis through the activation of intracellular signalling pathways, such as mitogen activated protein kinase (MAPKs), protein kinase B (Akt), Jun-N-terminal kinase (JNK) or c-Jun.
To investigate the ability of ET-1 receptor antagonist macitentan in contrasting the ET-1 induced activation of the intracellular signalling pathways involved in the profibrotic myofibroblast activity in cultured human normal dermal fibroblasts.
Design and Method. Cultured human dermal fibroblasts were obtained from skin biopsies of 4 healthy subjects (HSs, mean age 65±12 years) during diagnostic procedures and after signing informed consent. After serum starvation (18 hrs), cultured human dermal fibroblasts at 3rd culture passage were treated with ET-1 (100nM) alone and in presence of macitentan (10μM) for 30 minutes and 1 hr. Untreated cells were used as controls. The myofibroblast phenotype activation and ECM overproduction were investigated by immunocytochemistry evaluating the αsmooth muscle actin (αSMA), COL1 and FN protein expression. The phosphorylation of MAPKs Erk1/2, Akt, JNK, and c-Jun were investigated by Western blotting.
Results. ET-1 induced αSMA expression and increased COL1 and FN protein synthesis in cultured human fibroblasts compared to controls. Moreover, ET-1 induced the phosphorylation of Erk1/2, Akt, JNK and c-Jun in these cultured cells. Macitentan contrasted the phosphorylation of all these profibrotic intracellular signaling molecules primarily after 1 hr of treatment, determining also the downregulation of myofibroblast activity, through the reduction of αSMA, COL1 and FN protein expression.
Conclusions. These preliminary observations indicate as the blockage of the interaction between ET-1 and its receptors through the action of macitentan might downregulate the direct effects of ET-1 in activating those intracellular signalling pathways that contributes to the persistency of the myofibroblast phenotype, at least on skin fibroblasts from HSs.

Keywords: SSc fibrosis, ET-1 receptor antagonist, myofibroblasts.

12 – LECTURE: Balneotherapy and RMDs: when, where and how to choose

L7:1

BALNEOTHERAPY AND RMDs: WHEN, WHERE AND HOW TO CHOOSE

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Background. Balneotherapy (BT) is widely used in daily clinical practice in many European countries,Turkey, Israel and Japan as complementary therapy in different rheumatic diseases (RMDs).
Purpose. The aim of this overview was to discuss the current scientific evidence about the clinical efficacy, mechanism of action and cost-effectiveness of BT in RMDs.
Clinical Evidence. Various systematic reviews, meta-analyses and randomized controlled clinical trials (RCTs) support the beneficial effects on pain, function and quality of life of BT in lower limb of osteoarthritis. BT demonstrated its favorable effect in treating chronic low-back pain with a significant improvement on pain and functional impairments persisting until 6 months after the treatment. In fibromyalgia syndrome most of the available studies are methodologically flawed and have small sample sizes, however current data showed a significant improvement on pain and tender point counts at the end and after 3-6 months of a cycle of BT. In patients with ankylosing spondylitis and psoriatic arthritis there are encouraging results, although the existing studies are not strong enough to draw firm conclusions. Doubts persisting about the use of BT in rheumatoid arthritis.
A comparison between the various studies is problematic due to the differences in the methodology, in particular, the heterogeneity of the interventions (kind of mineral water, modality of application, ect) makes difficult to determine which form of BT is most effective. Furthermore, the studies comparing the different BT approaches (spa therapy, baths and mud-pack therapy) are scarse; the data available are insufficient to show the superiority of one of these techniques over another one.
Mechanism of Action: what is the evidence?: The mechanisms by which BT alleviates symptoms in RMDs are not fully clarified. The net benefit probably is the result of a combination of mechanical, thermal and chemical effects. Thermal stress induces a series of neuroendocrine reactions. BT decreases serum levels of prostaglandin E2, leukotriene B4, interleukin-1β, tumour necrosis factor-α, adiponectin and resistin, and enhance insulin-like growth factor-1 and transforming growth factor-β. *In vitro* and *in vivo* studies show the positive effect of mineral waters on the oxidant/antioxidant system. Overall, mineral waters or mineral components, in particular, hydrogen sulfide (H_2S), have a chondroprotective effects on chondrocyte or cartilage cultures.
Cost-effectiveness: The current literature on the cost-effectiveness of BT for RMDs is scarse. Van Tubergen et al. reported favorable cost-effectiveness and cost-utility ratios for combined spa–exercise therapy besides standard treatment in patients with ankylosing spondylitis. Zijlstra *et al*. in patients with fibromyalgia syndrome treated with a cycle of spa therapy demonstrated a temporary improvement of the disease associated with limited incremental costs per patient. Recently, an economic evaluation performed by an Italian group in patients with knee osteoarthritis showing a costs savings of about €672 per patient and 0.18 quality adjusted life years gained over 12 months follow in patients treated with BT in comparison to patients treated with usual care alone.
Conclusions. In conclusion, substantial pre-clinical and clinical evidence suggest that BT is an effective, well-tolerated and cost/effective complementary therapy for different RMDs.

13 – SIXTH SESSION: Systemic Lupus Erythematosus and related syndromes

S6:1

SYSTEMIC LUPUS ERYTHEMATOSUS: EPIDEMIOLOGY, NUTRITIONAL ASPECTS AND ENVIRONMENTAL FACTORS

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Purpose. Systemic Lupus Erythematosus displays remarkable immunological and phenotypic heterogeneity that arises from both genetic and non-genetic disease modifiers. Studying the epidemiology and associated risk factors provide important insights regarding the disease pathogenesis, primary and secondary prevention.
Methods. A critical review of the recently published literature on SLE epidemiology and environmental factors.
Results. Emerging data suggest a changing worldwide epidemiology of SLE with increased incidence and prevalence trends. Incidence of lupus nephritis seems to be rather stable while other forms of the disease (*e.g.* neuropsychiatric) demonstrate increasing trends. Notwithstanding improvement in overall medical care, the clinical, societal and financial burden of SLE remains high and a substantial proportion of patients develops irreversible organ damage. Apart from the increased awareness and recognition of the disease, a number of environmental factors such as tobacco and alcohol use, exposure to hormones, sunlight, solvents, pesticides, dyes and occupational metals, have been suggested to account for the increased frequency of SLE, however the supporting evidence remains circumstantial. To this end, recent studies have illustrated a possible role for the place of residence (urbanization), dietary micronutrients that can affect DNA methylation, and of the microbiome in the pathogenesis and/or progression of human or murine SLE.
Conclusions. While the effect of the environment on the development and prognosis of complex disease such as SLE is undisputable, further studies focusing at the early or pre-clinical stages of the disease will be required to establish the contribution of specific epigenetic/environmental factors.

S6:2

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) – THE EARLY DISEASE: CLINICAL FEATURES AND DIAGNOSTIC INVESTIGATIONS

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Systemic lupus erythematosus (SLE) is a multiorgan disease with protean manifestations. Because SLE is uncommon and heterogeneous, its diagnosis can pose a considerable challenge, especially for clinicians with limited expertise of the disease (1). This is particularly true at the early stages of SLE, when an inadequate number of features to secure the diagnosis might be present, and for patients presenting with uncommon features, which can nonetheless be severe and require prompt treatment. Thus, to date, the diagnosis of SLE remains clinical, guided by a constellation of clinical and serological manifestations. Most patients present with *systemic* but some with *organ-dominant disease* making diagnosis more challenging. To date, no diagnostic criteria for the disease exist reflecting both the complexities of the disease and medicolegal considerations. In this context, *classification criteria* are only to be used for classification of patients as they are imperfect for the diagnosis of SLE –especially patients with early disease. Strict adherence of classification criteria can result in significant diagnostic delays. Accordingly, in patients with severe major organ involvement who do not fulfill the criteria, treatment should not be delayed. Ongoing project (EULAR/ACR) to create a new set of classification criteria - using novel approaches - in order to improve recruitment to trials with novel drugs. Other efforts are focused in biomarkers for the early characterization of endotypes of the disease and personalized management. While eagerly awaiting diagnostic criteria for this disease, we have proposed interim potential solutions to facilitate its diagnosis (1).

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S6:3

MANAGEMENT: FROM GUIDELINES UP TO THE LAST TREATMENT ISSUES

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Many progresses have been made in treatment of patients with systemic lupus erythematosus (SLE), leading to better survival and better short term prognosis compared with the past (1). However, long-term prognosis still remains poor especially for patients experiencing major organ involvement.
Treatment strategies in patients with SLE are still mostly based on corticosteroids and immunosuppressants, often leading itself to organ damage, which is sometimes unavoidable due to the lack of novel drugs to be chosen and combined Corticosteroids have been and still represent the mainstay of SLE treatment. They have been among the few approved drugs for sixty years and have proved as life-saving drugs, yet they are associated with organ damage, namely preterm osteoporosis, diabetes, cardiovascular disease and accelerated organ failure.
Accordingly, several efforts have been made to introduce new drugs in SLE, but the barrage of traditional immunosuppressive drugs has not been overcome yet (2).
Currently, the only approved biologic drug for SLE is Belimumab, which was effective in two phase III randomized controlled trials (RCT) (3). Post-hoc analyses have also shown belimumab to be more effective in patients displaying a higher clinical and serological disease activity. Cumulative steroid dosage was shown to decrease along with belimumab continuation when compared with standard of care plus placebo. Apart from RCT and pooled analyses, real-life evidence also points to a true efficacy of belimumab in SLE both in terms of disease activity control and steroid reduction (4, 5).
Another emerging drug deserving attention is anifrolumab, targeting type I Interferon (IFN) receptor (IFNAR I), whose effectiveness in phase II RCT in non-renal SLE has recently been published, paving the way to further phase II and III RCT which are currently running in renal and non-renal lupus, respectively (6). Interestingly, patients in phase II trial were assessed their IFN-signature, *i.e.* the percentage of expression of a series of IFN-dependent genes, since those with a higher signature were expected to better respond. Actually, response of patients to anifrolumab was comparable, yet patients with a higher IFN signature were less likely to respond to placebo, thus suggesting that addition of targeted treatments even on a full standard therapy may make sense in patients who used to fall into the category of non-responders, maybe owing to an imbalance in their cytokine profile, which is likely to happen in SLE.
Ustekinumab is a monoclonal antibody that blocks the shared p40 subunit of the cytokines IL-12 and IL-23. It was approved for the treatment of psoriasis, psoriatic arthritis and Crohn's disease.
From an immunologic point of view, IL-12 is essential for TH1 cell development and IL-23 drives the expansion and survival of pathogenic TH17. IL-12 and IL-23/IL-17 axis have been implicated in the pathogenesis of SLE as shown by a number of studies on animal models, by genetic studies and studies in human tissues. In a phase 3 RCT, presented at 2017 ACR meeting in San Diego, Ustekinumab was superior to placebo (plus the SoC) in terms of SRI-4 response with a very promising size effect: 29%. Ustekinumab was particularly effective in patients with joint and mucocutaneous manifestations. Finally an increase in C3 and a decrease in anti-DNA antibody levels was shown in patients treated with Ustekinumab. Thus, after the failure of many RCTs, some successes have been achieved which open the avenue to new advances in this complex field

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S6:4

THE ANTIPHOSPHOLIPID SYNDROME: NEWS ON MANAGEMENT AND UNMET NEEDS

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The standard treatment of antiphospholipid syndrome (APS) remains a challenging topic to grasp. In fact the current management is based on long-term anticoagulation with vitamin K antagonist (VKA) to prevent the recurrence of thrombosis and the combination of low dose aspirin (LDA) and prophylactic dose of heparin to prevent recurrent miscarriages and obstetric complications. However, the management of APS in refractory cases remains an area of uncertainty, mainly due to the paucity of available data and of appropriate designed multicenter studies.
There is currently no clear consensus on the best approach on the management of patients with APS and arterial thrombosis or recurrent thrombotic events. There is a lack of prospective data demonstrating the superiority of high- or moderate-intensity anticoagulation with VKA over antiplatelet agents in the prevention of arterial thrombosis. Nevertheless, several small retrospective studies have shown that combination therapy (anticoagulant and antiplatelet) may reduce the risk of thrombotic recurrences in these patient. This requires further investigation with randomized prospective multicenter studies.
Another sensitive topic is the exact heparin dosage (prophylactic or full-dose anticoagulation) given in patients with Obstetric APS (O-APS) without history of thrombosis and refractory to standard therapy. Considering the weight-gain during pregnancy, do we need to adjust the heparin dose accordingly?
The primary prophylaxis to reduce the thrombotic and obstetric risk in individuals positive for antiphospholipid antibodies (aPL) without clinical manifestations of APS, the so called “aPL carries”, or positive for aPL with non-criteria clinical manifestations (*e.g.* thrombocytopenia) is still not clear and should be clarified in prospective studies.
The acute management of patients with catastrophic APS (CAPS) is based on anticoagulation, corticosteroids, plasma exchange and/or intravenous immunoglobulin administration according to expert opinion based on data from the CAPS Registry. The use of Rituximab and Eculizumab have been successfully reported in isolated cases of CAPS. Prospective trials should be carried on to test the efficacy and the best therapeutic approach.
Novel direct oral anticoagulants are under investigation also in APS, but the might be not as effective as VKA, especially in patients with previous arterial events.
As traditional cardiovascular risk factors increase the risk of thrombosis related to APS, the role of statins is of particular interest because of the dual functions of inhibiting cholesterol synthesis and modulating inflammatory response. It has been reported that Fluvastatin reduces inflammatory and pro-thrombotic markers in individuals aPL positive and pravastatin improves pregnancy outcomes in a cohort of pregnant APS women with pre-eclampsia and intrauterine growth restriction but the evidence is still scarse.
Recent experimental data and retrospective studies suggest a protective role of hydroxychloroquine (HCQ) to prevent thrombosis and obstetric complications. The randomized controlled trial of HCQ *vs* placebo in pregnant women positive for aPL will provide scientific evidence on the efficacy of HCQ in reducing the risk of obstetric complications in APS and aPL carriers.
Despite the recent improving in the understanding of pathogenic mechanisms, the management of APS patients remains challenging in many aspects. This indicates the need of further prospective and controlled studies to find sound therapeutic approaches in APS patients.

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14 – Systemic Lupus Erythematosus and related syndromes

OC6:1

TRANSCRIPTIONAL REGULATION OF BAFF-R, BCMA AND TACI BY MIR-873 AND MIR-1976 IN JUVENILE SLE

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Objective. Systemic lupus erythematosus (SLE) is a complex autoimmune disorder characterized by hyperactivated B-cells. B-cell activating factor (BAFF) affects the survival, differentiation and function of B-cells by binding to its B-cell receptors BAFF-R, BCMA and TACI, and new therapies are targeting this pathway. microRNAs (miRs) are endogenous non-coding RNAs which post-transcriptionally regulate thousands of genes, and are currently in clinical trials for their use as therapeutic entities. This study aimed at identifying miRs which may regulate BAFF-R, BCMA and TACI.
Design and Method. Bioinformatics was used to predict miRs targeting BAFF-R, BCMA and TACI. Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of 42 Egyptian juvenile SLE (jSLE) patients and healthy age-matched controls using ficoll. PBMCs were transfected with oligonucleotides using HiPerfect. RNA was extracted using Bizol reagent then the relative expression of miRs and mRNA was analyzed by qRT-PCR. Levels of B-cell-specific CD19 protein were analyzed by flow-cytometry.
Results. Bioinformatics revealed that miR-873 potentially targets both BAFF-R and BCMA while BAFF-R and TACI may be targets for miR-1976. Both miR-873 and miR-1976 were overexpressed in PBMCs of jSLE patients compared to controls (p=0.0335* and p=0.0266*, respectively). Conversely, BAFF-R, BCMA and TACI were underexpressed in patients (p=0.0101*, p=0.035*, and p=0.0468*, respectively). Positive control knockdown of BAFF-R, BCMA or TACI by transfection of specific siRNAs into PBMCs of jSLE patients caused extensive repression of the three receptors (p=0.0328*, p=0.0377*, and p=0.0470*, respectively) compared to mock untransfected PBMCs. Ectopic expression of miR-873 suppressed BCMA expression (p=0.032*), and miR-1976 downregulated TACI expression (p=0.0399*) compared to mock untransfected cells. On the other hand, both miR-873 and miR-1976 restored BAFF-R expression (p=0.0104* and p=0.01**, respectively). Despite this, both transfection of miR-873 or miR-1976 mimics decreased the levels of CD19 protein, a protein which is contained in the B-cell receptor complex, regulating its activation threshold and playing critical roles in autoantibody-secreting B-cell differentiation.
Conclusions. These findings suggest that the aberrant expression of miR-873 and miR-1976 may play a role in SLE pathogenesis through regulating BAFF-R, BCMA and TACI mRNA and CD19 protein levels, and may provide an attractive therapeutic outlet for the treatment of SLE.

Keywords: emicrorna, BAFF receptors, juvenile SLE.

OC6:2

THROMBOSPONDIN-1 IS ELEVATED IN THE PLASMA OF PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME AND IS CORRELATED WITH FREE ACTIVE TGF-B1 LEVELS, IL-1B AND IL-17A

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Objective. Thrombospondin (TSP1) is a matricellular glycoprotein secreted by platelets upon activation with proinflammatory, antiangiogenic and pro-apoptotic properties. TSP1 activates TGF-b1 and has been shown to be involved in TH17 response. We aimed to investigate the role of TSP1 in antiphospholipid syndrome (APS).
Design and Method. The study involved 90 APS patients, 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 (HUVECs) 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 supernatants were used to stimulate $CD4^+$ T-cells. Plasma and cell culture supernatants were analyzed for the presence of TSP1, IL1b, IL17A and free active TGF-b1 levels by ELISA.

Results. APS patients had higher plasma levels of TSP1 than HCs and SLE patients (APS: mean 390 ng/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 TSP1 (r=0.827, $p<0.0001$). Among the APS patients those with TSP1 levels >600ng/ml had detectable IL1b and IL17A in their plasma. APS-HUVECs cultured under standard conditions and HC HUVECs cultured with APS plasma expressed higher levels of TSP1 than HC HUVECs 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 IL1b and TSP1 compared to the ones stimulated with HC IgG (700 vs 50pg/ml and 500 vs 200ng/ml respectively). APS stimulated supernatants induced the expression of IL17A from healthy donor T cells (250pg/ml) whereas the HC had no effect. Patients with APS and pregnancy morbidity alone expressed lower TSP1 levels (130.1ng/ml) than APS patients with miscarriages and thrombosis (403.2ng/ml).
Conclusions. APS patients express higher TSP1 plasma levels correlating with free active TGFb1. Monocytes and HUVECs treated with APS-plasma and APS IgG produce higher levels of TSP1 and IL1b and these supernatants induce the expression of IL17A from naïve T-cells. All these suggest a possible involvement of TSP1 in thrombus formation, inflammation and inhibition of angiogenesis that needs further study.

Keywords: thrombospondin-1, antiphospholipid syndrome, plasma.

OC6:3

HYDROXYCHLOROQUINE DOSING: DOES BY IDEAL BODY WEIGHT OR GROSS WEIGHT MAKE A DIFFERENCE?

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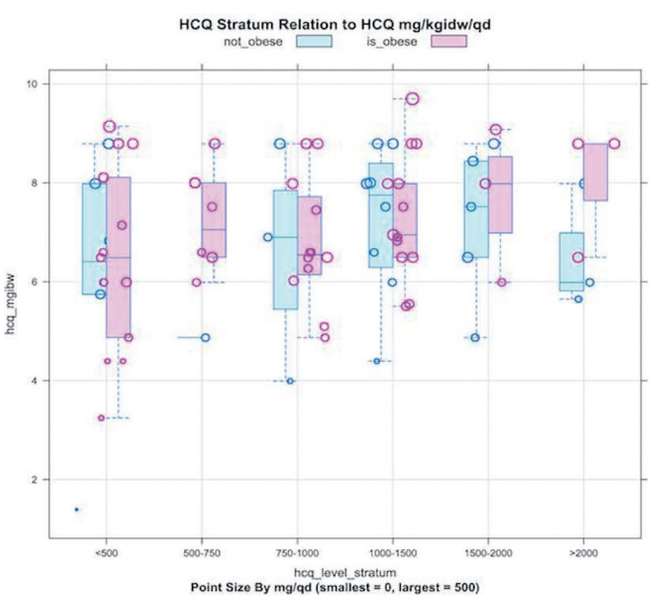
Objective. 1. To find out whether Hydroxychloroquine (HCQ) dosing, by ideal body weight (IBW) vs gross weight (GBW) without addressing obesity issue, makes a difference in achieving the target level.
2. Whether the drug level correlates with therapeutic effect in systemic or cutaneous lupus, lupus or other inflammatory arthritis.
3. Our clinic always uses 6.5 mg / kg IBW. American Academy of Ophthalmology recommends 5mg/GBM regardless of obesity for safety purpose. We set to find out whether IBW formula dosing is still adequate.
Design and Method. 1. Observation over 70 ambulatory patients on HCQ, from February to December 2017, blood HCQ and proximate creatinine level and medical records reviewed to include their gender, age, diagnosis, disease activity measurement by SLEDAI 2K for lupus, CDAI for polyarthritis, or other variables as applicable.
2. Statistical analysis performed using Multi-Ordinal Regression.
Results. See Graph



1. Using BMI 30 criteria we find over 50% patients are obese.
2. IBW dosing not over 400mg/day, with obesity, is significantly more likely to have HCQ levels < 500. ($p<0.01$)
3. IBW and GBW are reasonably equivalent in reaching therapeutic range. Therapeutic effect tends to correlate with higher drug level: best at >1000, still better at 750-1000. Closest significance for the 1500-2000 strata is an odds ratio of 1.90 ($p=0.155$)
4. Obesity is significantly less likely to have levels >2000 ($p<0.01$)
5. High creatinine tends to, but not significantly, associate with high HCQ level
Conclusions. 1. For non-obese patient, with BMI <30, both IBW and GBW work equally well in achieving target level.
2. With IBW dosing, obesity is likely resulted in low drug level but unlikely result in high level.
3. Hydroxychloroquine level over 750-1000 anticipates favorable therapeutic effect.
4. For obese patients, IBW as well as capping at 400mg, limits the ability to compensate the overweight issue; therefore testing the hydroxychloroquine level is advisable.
5. Noncompliance results in low level, but the reverse is not proven here.

Keywords: lupus erythematosus, hydroxychloroquine, drug level.

OC6:4

AVEMAR, A NEW BENZOQUINONE CONTAINING NATURAL PRODUCT IN SLE PATIENTS TREATMENT

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Objective. A Fermented Wheat Germ Extract with standardized benzoquinone content (Avemar) is able to improve clinical and laboratory parameters in mice subject to SLE (1). Authors postulate that results may be related to a rebalancing of the lymphocyte subclasses Th1/Th2 (inhibition of IL4 and IL10 production). FWGE has significant anti-inflammatory efficacy confirmed by plethysmography, histology, and real-time PCR in Wistar rat adjuvant arthritis (AA), a relevant animal model of human RA (2). It has also been shown that FWGE upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell. Moreover, FWGE also inhibits cyclooxygenase (COX)-1 and -2 and thus has anti-inflammatory activity. This product contains large amounts of quinolonics and flavonoids. It is therefore likely that the immunomodulatory therapeutic effect can be ascribed to them.
Based on these clinical with a complete lack of toxic side-effects, a double-blind clinical study with Avemar in SLE patients has been performed.
Patients and Methods. In a placebo controlled randomized double-blind we compare the effect of best conventional therapy plus a continuous Avemar administration against best conventional therapy on its own in SLE patients of various clinical stages. Thus the primary endpoint of the study was to test Avemar's efficacy in the treatment of lupus by means of clinical score activity index SLEDAI. The secondary endpoint was to verify the efficacy of Avemar in 1) preventing and/or treating premature atherosclerosis; 2) preventing osteoporosis; 3) rebalancing the lymphocyte subclasses Th1/Th2 (inhibition of the IL4 and IL10 production); and 4) modulating the expression of HLA class I molecules of lymphocytes in reducing oxidative stress. Inclusion criteria: SLE patients under treatment with steroids, antimalarial therapy, cytotoxic drugs. Exclusion criteria: Asymptomatic patients currently under observation without any therapy. Randomisation criteria: a total of 100 patients are to be enrolled and divided, according to a randomization list, into four groups receiving either 9 or 18 g/day of Avemar or placebo for one year.
Preliminary reports: After 6 months the decrease of the SLEDAI score was significant in the Avemar group in comparison of the placebo group.

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Keywords: nutraceutical, antioxidant, SLE.

OC6:5

ANTIPHOSPHOLIPID SYNDROME: REVIEW OF 52 CASES OF A PORTUGUESE RHEUMATOLOGY DEPARTMENT

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Objective. Antiphospholipid Syndrome (APS) is an acquired disorder associated with autoantibodies against phospholipids and binding protein complexes. It is defined by the presence of two major components: 1) occurrence of at least one of the following clinical manifestations - thrombosis (venous or arterial) or morbidity in pregnancy. 2) presence of at least one type of antiphospholipid autoantibody in the plasma (Sapporo *et al*., 2006)
This entity can be classified as primary or secondary and, in the latter case, is more frequently associated with Systemic Lupus Erythematosus (SLE).
The aim of this study was to characterize demographic, laboratorial and clinically the set of patients with APS, followed in our rheumatology department.
Design and Method. Retrospective evaluation of the clinical processes, discharge charts and rheumatic records of patients followed in the Rheumatology Department between 2005 and 2017, with the diagnosis of APS, according to the Sapporo Criteria.
Results. A total of 52 patients were identified, most of them female (88.5%). The mean age at diagnosis was 35.7±13.24 years. About 71% of the cases corresponded to secondary SAF, all of them associated with SLE. 29% of patients had primary APS.
Regarding the clinical manifestations, 80.8% of the patients presented thrombotic events, 7.7% complications in pregnancy and 11.5% presented both (thrombotic events and pregnancy complications). Of the patients who presented thrombotic events, 54.2% had Deep Venous Thrombosis (DVT) as the 1st thrombotic event. 80% of complications in pregnancy occurred after 10 weeks of gestation.
Laboratorial investigation revealed the presence of lupus anticoagulant in 75% of patients and anti-cardiolipin and anti-beta2-Gliprotein I antibodies in 46.2% and 40.3% of patients respectively.
The most common identified cardiovascular risk factors were hypertension (34.6%) and dyslipidemia (38.5%). The majority of patients with thrombotic events were anticoagulated.
Conclusions. In this cohort, the majority of the patients were female and presented secondary APS (in all cases in association with SLE). Vascular thrombotic events were the most frequent clinical manifestation, with prominence for DVT (both as the first event and in the overall thrombotic events). The clinical and laboratory characteristics described in this cohort are in agreement with those previously described in other studies.

Keywords: antiphospholipid, thrombosis, pregnancy.

OC6:6

OUTCOME OF ADULT PATIENTS WITH CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS AND JUVENILE IDIOPATHIC ARTHRITIS IN A SINGLE COHORT

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Objective. To report the long-term outcome including disease activity and damage in addition to the social, quality of life in adults with childhood-onset systemic lupus erythematosus (cSLE) and juvenile idiopathic arthritis (JIA) in a single cohort.
Design and Method. All adult patients with cSLE and JIA who treated and had regular follow-up between 1990 and 2016 at King Faisal Specialist Hospital and Research Centre (KFSH-RC), Riyadh were included. The disease status, social, educational and employment history, as well as long-term outcome measures, comprised SLE Disease Activity and Damage Indices and Juvenile Arthritis Multidimensional Assessment Report (JAMAR), Juvenile Arthritis Damage Index (JADI) were obtained at the last follow-up visit.
Results. Total of 88 patients were included, 48 patients (45 female) had cSLE with a mean age of 23.6+4 years while the mean disease duration was 15+4 years and 40 (27 female) had JIA with a mean age of 21.9±6 years and the mean disease duration was 15±6 years. At the last follow-up visit, 24 (50%) cSLE patients were found to have active disease with a mean of accrual damage index of 2 (0-7). Forty patients (83%) had renal involvement, 7 (15%) of them progressed end-stage renal disease, 5 patients underwent renal transplant and 16 patients had central nervous system involvement. Of the 40 JIA patients, 45% had polyarticular subtype and 42% had systemic JIA. At the last follow up visit, 87% of the patients were in clinical remission. The mean JADI was 9.4±9 and mean damage joints was 4.8±4. The mean functional ability scale was 5.6±5 and health-related quality of life was 6±4. Forty-three cSLE patients completed high school and 21 joined a college. Six patients had work. Eight patients got married and 5 of them had children, while 26 JIA completed high school and 11 joined a college. Seven patients had work and 5 got married, all had children.
Conclusions. Most of our patients with cSLE had active disease with multiorgan involvement while patients with JIA had a quiescent disease. However, outcomes were satisfactory and comparable to earlier reports.

Keywords: outcome, childhood-onset systemic lupus, juvenile idiopathic arthritis.