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E-POSTER DISCUSSION 01: COVID
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ANTINEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVITY INCIDENCE BEFORE AND DURING COVID19 PANDEMIC

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Background and Aims: There are some pathogenetic similarities between antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) and COVID19 disease. Production of ANCA in COVID19 patients, without clinical criteria for diagnosis of AAV, could be mediated by a molecular mimicry and cytokine storm. Our aim was to compare incidence of positive ANCA results before (BP) and during (DP) COVID19 pandemic.

Methods: We retrospectively analyzed serum levels of proteinase 3 ANCA (PR3-ANCA) and myeloperoxidase ANCA (MPO-ANCA) determined by multiplex immunoassay. Positive ANCA results were compared in two years (2018 and 2019) BP and (2020 and 2021) DP.

Results: 20983 results were analysed, 10491 PR3-ANCA and 10492 MPO-ANCA. 2.78% positive results were detected in total. Both PR3-ANCA and MPO-ANCA were more commonly ordered DP. Considering PR3-ANCA, 169 of 5140 (3.29%) positive results were detected BP and 209 of 5351 (3.91%) DP ($p=0.044$). Considering MPO-ANCA, 116 of 5139 (2.26%) positive results were detected BP and 90 of 5353 (1.68%) DP ($p=0.016$). Positive MPO-ANCA results were the most common in the elderly (4.06%). In 25 cases ANCA assays were ordered during COVID19 infection and only one patient had a positive result of PR3-ANCA (4%).

Conclusions: There were more positive PR3-ANCA results DP, compared to MPO-ANCA results which were more commonly positive BP. It is unclear if COVID19 could trigger development of AAV, but it could induce the production of PR3-ANCA. Less than 3% positive results indicate the need for more rational use of this serological test.

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PREVENTION OF SEVERE COVID-19 AMONG AUTOIMMUNE INFLAMMATORY RHEUMATOID DISEASES (AIRD) PATIENTS BY THE 3RD AND 4TH BOOSTER BNT162B2 MRNA VACCINES DURING THE OMICRON OUTBREAKS

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Background and Aims: We aimed to assess the contribution of the 3rd and 4th booster mRNA vaccines against SARS CoV2, in preventing severe COVID-19, in AIRD patients (pts) treated with immunomodulating drugs.

Methods: 202 pts (mean age(SD) 57(13), disease duration 11.2(7.4), who received the 3rd booster (Pfizer) were included in the study. We performed serology test 24 weeks after receiving the second dose of vaccine and 4-8 weeks after the 3rd booster. IgG Antibodies (Ab) against SARS COV2 virus were detected using the SARS-Cov-2 IgG II Quant (Abbott) assay. The test was considered positive above 50 AU/ml. Data regarding COVID-19 infection during the 5th outbreak (omicron) were collected from the medical files.

Results: The 3rd booster administration (Pfizer) significantly augmented the humoral response (from mean(SD) 1121(4723)AU/ml to 12153(13687)). 65 pts (32%) had COVID-19 within mean(SD) 163.3(34.5) days after 3rd booster vaccination. 12 pts (24%) out of 50 who received the 4th booster, contracted COVID-19 within mean(SD) 37.2(24.6) days after the vaccination. Only 2 pts (rituximab treated) had severe COVID-19. There were no statistically significant differences between the pts with COVID-19 to those without, regarding age, type of disease, treatment and humoral response.

Conclusions: An enhanced humoral response was obtained after the 3rd booster. 32% of AIRD pts vaccinated with 3 doses and 24% of pts vaccinated with 4 doses had COVID-19 during the omicron outbreak. The booster vaccines conferred 99% protection against severe COVID-19.

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ANALYSIS OF ANTI-SARS-COV-2 ANTI-SPIKE PROTEIN RECEPTOR BINDING DOMAIN (RDB) IGG LEVELS IN A COHORT OF PATIENTS AFFECTED BY SYSTEMIC AUTOINFLAMMATORY DISEASES RECEIVING IL-1 INHIBITORS

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Background and Aims: The pro-inflammatory cytokine cascade typical of systemic autoinflammatory diseases (SAIDs) may present with similar characteristics in severe forms of SARS-CoV-2 infection. That is the reason why anti-IL-1 drugs have been successfully employed to treat COVID-19. In this study, we evaluated the antibody response after SARS-CoV-2 vaccination in patients on IL-1 inhibitors and not, compared to a group of healthy vaccinated controls (HC). We also evaluated the COVID-19 clinical course in a subgroup of patients between 2020 and 2022.

Methods: In 47 patients (mean age 48.4 ±13.9 years), the serological response was assessed using the CLIA MAGLUMI™ 2000 Plus test, 40 days and six months after the first vaccination cycle and after the booster dose. Fifty-five fully vaccinated healthcare workers were enrolled as HCs. *GraphPad Prism 5* software was used for statistical analysis.

Results: All vaccinated patients developed an adequate antibody response (>33 BAU/L). No significant differences were observed between the antibody levels developed by patients receiving IL-1i compared to those not on anti-IL-1 after the first vaccination cycle (p= 0.98) and after the booster dose (p=0.50). The mean antibody titer after the booster dose was not different in SAIDs compared to HCs (p=0.66). SAIDs/COVID-19 patients on anti-IL-1 had a benign course without experiencing severe symptoms nor disease relapses.

Conclusions: Anti-IL-1 drugs and colchicine do not alter the antibody production after vaccination, which is comparable to the response observed in HCs. In addition, the inhibition of the IL-1 axis may “protect” infected subjects from developing more severe clinical consequences related to hyperinflammation.

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SARCOIDOSIS AND COVID-19: IMMUNOLOGICAL RESEARCH EXPERIENCE

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Background and Aims: **Background and Aims:** SARS-CoV-2 can be a trigger factor of autoimmune reaction when sarcoidosis that activates progression of the disease. The aim of this study is to define the level of immunological parameters in patients with pulmonary sarcoidosis after COVID-19.

Methods: The serum samples of patients with sarcoidosis (SD) (n = 52), a control group (n= 30) (healthy subjects) were collected from 2017 to 2022 year (men, n = 30 (57.7%), women, n = 22 (42.3%)) were examined. We divided patients into three groups: I group (n= 34) – SD (+) COVID-19 (-) in anamnesis; II group (n= 18) – SD (+) COVID-19 (+) in anamnesis; III group (n=30) – control group. Circulating 'polarized' T-helper cell subsets were analyzed by multicolor flow cytometry.

Results: We found that within CD45RA–CCR7+ central memory cells SD(+)-COVID-19(+) patients had increased levels of Th2 cells vs. SD(+) and HC (11.40% vs 8.92 and 7.21% with p=0.008 and p<0.001, respectively). Furthermore, SD(+)-COVID-19(+) patients showed increase levels of Th1 cells and decreased frequencies of Tfh cell vs. SD(+) patients (11.20% vs. 8.11% with p=0.003 and 31.34% vs. 39.66% with p<0.001, respectively). Finally, SD(+)-COVID-19(+) and SD(+) groups had decreased levels of Th17 cells in compared to HC (34.12% (28.11; 38.08) and 36.28% (29.64; 40.41) vs. 80.39% (35.41; 47.79) with p=0.016 and p=0.009, respectively).

Conclusions: Thus, we showed an imbalance within almost all circulating memory Th subsets in patients with pulmonary sarcoidosis after acute COVID-19. Our data will help us better understand the pathogenesis of post-COVID-19 sarcoidosis.

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OPTIMISE - VALIDATION OF THE SLEDAI-P SELF-QUESTIONNAIRE COMPLETED BY THE PATIENT TO MEASURE THE ACTIVITY OF THE SYSTEMIC LUPUS

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Background and Aims: Systemic Lupus Erythematosus (SLE) is a rare and chronic autoimmune disease. Disease activity (DA) is marked by remissions, spontaneous relapses or induced by therapeutic modifications. SLE exposes to serious complications requiring close medical follow-up, but flares cannot be predicted and often do not coincide with medical consultations. SLE DA is measured during a consultation using the SLEDAI tool, but cannot be completed by patients. There is therefore high at stake to develop tools allowing patients to measure DA, predict flares and subsequently tailor the medical follow-up to each patient. Using the same framework as a previous nationwide study related to COVID-19 impact (EPICURE survey), we aim to develop and validate, in collaboration with the french national Lupus Reference Centers and Hometrix Health, a patient-tailored tool (SLEDAI-P).

Methods: SLEDAI-P was designed by expert lupulogist and patients. It consists of simple patient-oriented questions allowing numerical score calculation. To validate the SLEDAI-P, we will recruit 500 SLE patients who satisfy 2019 ACR/EULAR classification criteria. Patients will complete the self-questionnaire and have a clinician follow-up within 7 days. The SLEDAI-P validity will be assessed by calculating the correlation between SLEDAI-P and SLEDAI-2K provided by the clinician (blindly of the SLEDAI-P results). Quality of life via SF-36 will evaluate if SLEDAI-P predicts patient-reported-outcome-measures.

Results: The results of this survey will permit the validation of the SLEDAI-P as a self-questionnaire carried by the patient.

Conclusions: The self-administered questionnaires such as the SLEDAI-P may allow better tailored treatment and follow-up, empower SLE patients for control and management of their disease.

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PERSISTENT AUTOIMMUNITY POST-COVID-19 : A PROSPECTIVE COHORT STUDY

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Background and Aims: Since the onset of the COVID-19 pandemic, several reports have highlighted the link between the SARS-CoV-2 infection and autoimmunity, resulting in the production of multiple autoantibodies and the occurrence of autoimmune diseases. Autoimmunity has also emerged as one of the pathophysiological mechanisms of the post-COVID-19 syndrome. There are few studies on the link between persistent autoimmunity post-COVID-19 and pulmonary sequelae, particularly lung fibrosis.

Methods: Patients who were previously hospitalized with COVID-19 pneumonia were prospectively included at 3 or 4 months after the onset of symptoms. Patients underwent lung functional test, chest computed tomography imaging and screening of different autoantibodies such as antinuclear antibodies, antiphospholipid antibodies [lupus anticoagulant (LA), anticardiolipin (ACL) and anti-b2 glycoprotein I antibodies (ab2GPI)], ANCA and anti-annexin A2 antibodies (aANXA2). For all patients, we collected demographic data (age, sex).

Results: We included 101 patients with a male predominance (68 male and 33 female). The median age was 67 [20-90] years. Lung involvement have been observed at 3-4 months in 69 patients. The carbon monoxide diffusing capacity of the lung was reduced in 26% of patients. The prevalence of AAN, ACL, ab2GPI, ANCA, aANXA2 and LA was 13.6%, 7.7%, 5.9%, 3.9%, 6.6% and 2.1% respectively. We observed at least one autoantibody in 33.7% of patients. The positivity of AAN was observed in 16.6% of patients having pulmonary sequelae with ground glass opacities.

Conclusions: Our study showed persistent autoimmunity post-COVID-19, mainly represented by AAN. Further long-term studies will be necessary to better define the involvement of these autoantibodies in pulmonary sequelae post-COVID-19.

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**CYTOCHROME P450 GENES EPIGENETIC PROFILE MAY EXPLAIN HIDRADENITIS
SUPPURATIVA RESISTANCE TO THERAPIES**

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Background and Aims: Hidradenitis suppurativa (HS) is a poorly characterized chronic inflammatory disease frequently unresponsive to medical treatments, and for which no baseline biomarkers of drug resistance have been identified. However, cytochrome P450 (CYPs) enzymes play a pivotal role in drug-metabolism, providing intriguing epigenetic promise for insight into the disease's etiology.

Methods: In this study we compared 24 HS patients with 24 age-, sex-, ethnicity- matched controls. DNA samples were extracted from peripheral blood samples and analyzed using the Infinium Methylation EPIC BeadChip array to detect methylation profiles in CYP genes. Then, data were visualised with a heatmap further analysed with principal component analysis to verify the clustering. Biological functional enrichment and functional protein association network were performed to characterised functional aspects of the results.

Results: A total of 13 differently methylated CpG sites (p -value < 0.05 and methylation differences ± 0.05) of 13 unique CYPs (11 hypomethylated, 2 hypermethylated) were found only in HS patients. The most significant association was in the *CYP19A1* encoding the aromatase enzyme involved in estrogen biosynthesis. The *CYP26* subfamily (*CYP26C1*, *CYP26B1*, and *CYP26C1*) are involved in retinoid acid metabolism, *CYP2C19* in clopidogrel resistance, *CYP2R1* affects Vitamin D deficiency while *CYP2C19* is linked to depression, resistance to antidepressants and suicide ideation.

Conclusions: Taken together, these results suggest that CYPs methylation profiles may identify new endotypes resistant to specific therapies in HS, introducing a new era of precision medicine. CYPs may also become future targets for treating HS more efficiently.

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**SELECTIVE SILENCING OF DISEASE-ASSOCIATED B LYMPHOCYTES FROM
HASHIMOTO'S THYROIDITIS PATIENTS BY CHIMERIC PROTIEN MOLECULES**

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Background and Aims: Hashimoto's thyroiditis is one of the most common endocrine disorders affecting up to 20% of the adult population. No treatment or prevention exists except hormonal substitution of hypothyroidism. We hypothesize that it may be possible to suppress selectively anti-thyroglobulin (Tg) IgG antibody producing B lymphocytes from HT patients by a chimeric protein molecule containing a monoclonal antibody specific for the human inhibitory receptor CR1, coupled to peptide epitopes derived from Tg protein. We expect that this treatment will down-regulate B cell auto-reactivity by delivering a strong inhibitory signal.

Methods: Three peptides – two epitope-predicted ones derived from Tg and another irrelevant peptide – were synthesized and then coupled with monoclonal anti-human CR1 antibody to construct three chimeric molecules. The binding to CD35 on human B cells and the effects of the chimeric constructs on PBMC and TMC from patients with HT were tested using flow cytometry, ELISpot assay and immunoenzyme methods.

Results: We found that after the chemical conjugation all chimeras retained their receptor-binding capacity and the Tg epitopes could be recognized by anti-Tg autoantibodies in the patients' sera. This treatment down-regulated B cell autoreactivity and cell proliferation, inhibited Tg-specific B cell differentiation to plasmoblasts and promoted apoptosis to the targeted cells.

Conclusions: The treatment of PBMCs from HT patients with Tg epitope-carrying chimeric molecules affects the activity of Tg-specific autoreactive B lymphocytes delivering to them a strong suppressive signal.

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EFFICACY AND SAFETY OF DUPILUMAB IN PATIENTS WITH REFRACTORY EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

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Background and Aims: Eosinophilic granulomatosis with polyangiitis (EGPA) is an ANCA-associated vasculitis characterized by asthma, blood and tissue eosinophilia and systemic manifestations. Dupilumab, a monoclonal antibody directed against the IL-4/IL-13 receptor, has been approved for eosinophilic asthma and chronic rhino-sinusitis with nasal polyposis, raising the question of its efficacy and tolerance in EGPA

Methods: Retrospective study including patients with EGPA fulfilling 2022 ACR/EULAR classification criteria and treated with dupilumab. Safety and efficacy were assessed. Complete response was defined by BVASv3=0 and prednisone dose \leq 4 mg/day, and partial by BVASv3=0 and prednisone dose $>$ 4 mg/day

Results: Eleven patients were included, 52.5 (45.3-57.0) years old, 36.6% female, 45.5% ANCA-MPO positive. Dupilumab was started for refractory ear-nose-throat manifestations. Median follow-up was 7.7 (4.4-13.1) months. Complete response was achieved in 45% of patients, while partial in 36%. Median BVAS was 3 (0.5-4) at dupilumab initiation, dropped to 0 (0-0) at 6 months. Baseline prednisone dose was 10 mg/d (5-15), decreased to 5 (0.6-5) at 6 months. Four patients reported adverse events (AE). Main AE were mild-to-moderate and included headache (n=1), injection-site reaction (n=1) and myalgia (n=2). Two patients discontinued dupilumab due to symptomatic hypereosinophilia. Dupilumab-induced eosinophilia was reported in 5 patients (45.5%), with a peak eosinophil count of 1500/mm³ (1200-2900) after 13 weeks (4-13) of dupilumab. No death was reported

Conclusions: Dupilumab was associated with frequent mild-to-moderate AE, and induced eosinophilia in half of patients, frequently transient and asymptomatic. A clinical benefit was noted in most patients. Dupilumab could therefore be an alternative therapeutic option in selected patients refractory to anti-IL-5 drugs

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GENDER DIFFERENCES IN A RARE DISEASE: ANALYSIS OF A MONOCENTRIC COHORT OF 100 PATIENTS WITH GIANT CELLS ARTERITIS.

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Background and Aims: Giant Cells Arteritis (GCA) usually occurs in patients older than 50 years. Epidemiological studies shown a higher prevalence in women compared to man. Differences in clinical presentation between men and women have not been demonstrated. This study aims to analyze differences in the clinical presentation of GCA according to sex.

Methods: We collected retrospectively clinical data of a monocentric cohort of 100 consecutive GCA patients.

Results: One-hundred patients with clinical diagnosis of GCA were enrolled (68 women, 32 men). Patients were classified according to vascular involvement in groups: temporal arteritis (C-GCA), extracranial large-vessel vasculitis (LV-GCA) and both cranial and extracranial vasculitis (LV-C-GCA). No significant differences in vascular distribution were found according to sex, even if large-vessel involvement seems to be more frequent in women (43% vs 28%; p:ns). Male and female patients presented a similar clinical picture, with the same frequency of systemic symptoms (fever, fatigue, weight loss), polymyalgia rheumatica, visual symptoms and claudication. However, male patients complained more often temporal headache (90% vs 71%, p:0.01), even no significant differences were found in the incidence of pathological findings at temporal artery physical examination (38% vs 32%; p:ns) and biopsy (59% vs 50%). On the contrary, in female patients a longer time to diagnosis was recorded (8(2-49) vs 4(0-35) months; p:0.01).

Conclusions: In our cohort, clinical presentation was similar in male and female patients, with no significant differences in clinical, radiological and laboratory findings. However, male patients presented more often temporal headache, the most typical symptom of GCA, and this could explain a shorter time to diagnosis.

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IN ZIMBABWE, THE PREVALENCE OF SYSTEMIC SCLEROSIS-SPECIFIC AUTOANTIBODIES IS HIGHEST IN THE 2010-2020 BIRTH COHORT. WHAT ARE THE AETIOLOGY, TREATMENT OPTIONS AND PROGNOSIS?

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Background and Aims: Although systemic sclerosis (SSc) is reportedly sporadic in children, we recently reported that 18% of 240 patients, aged 6 (95% CI=3.9-8.8) years, had SSc-specific autoantibodies (Abs). >90% of patients produce disease-specific-Abs with geographical and racial variations. We describe patient characteristics.

Methods: Clinical, laboratory and spirometry records of children seen between January 2016-December 2022 were reviewed and analysed. For autoantibody detection, a fixed 13-antigen immunoblot panel (Euroimmun) was used. The *Koko Sx1000* spirometer was used.

Results: The 1305 patients, including 287 with a mean age of 8.67 (95%CI 8.0-9.27) years, were investigated for SSc-specific autoantibodies. Eighty-nine (31%), mean age was 8.46 (95% CI 7.36-10.24) years were SSc-specific autoantibody-positive. The highest SSc-specific autoantibody reactivity (29%) was in the 2010-2020 birth cohort, aged 3.92 (95%CI 3.6-4.25), followed by the 2000-2009 cohort (27%) aged 12 (95%CI 11.42-12.62) years. Cutaneous, respiratory and gastrointestinal predominated. Pigmentary changes, arthralgia, Raynaud's, bloating, GERD and constipation were frequent, as were cough, dyspnoea and abnormal lung function values. The spirometry pattern was restrictive: FVC(75.63%), FEV1(75%) and PEFr(69.61%) . Detected autoantibodies were anti-RNA polymerase III-155kD(42.7%), anti-Th/To(35.95%), anti-RNA polymerase III-11kD(30%), anti-Ku(18.4%) and anti-CENP-B(6.7%). The dc-SSc were anti-Scl-70(5.6%), anti-fibrillarin(*U3 RNP*)(19.1%) and anti-NOR90 (12.35%). Anti-PMScl100 and anti-PMScl75 were detected in 3.37%and 11.2%, respectively.

Conclusions: The presentation reports the highest incidence of SSc-specific autoantibodies amongst symptomatic Zimbabwean children aged 0-10 years. In 33% of the children, autoantibodies were detected before four years. The type and frequency of antibodies differ from other populations. Anti-Scl 70 and anti-centromere were infrequent. The antibody prevalence has increased since the 1990s. Pertinent questions relate to the aetiology, diagnosis, treatment options and prognosis.

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TWO AUTOANTIGENIC ABDOMINAL AORTIC MATRIX COMPONENTS (AAP-40 AND COLLAGEN XI-ALPHA-1) ARE FIBRINOGEN-RELATED PROTEINS (FREPS)

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Background and Aims: Patients with Abdominal Aortic Aneurysms (AAA) have features of autoimmunity to microfibrillar components of the outer medial and adventitial regions of the normal aortic wall. Two antigens have presently been identified. Aneurysm Associated Antigenic Protein-40 kDa (AAAP-40) was detected by probing a tryptic digest of normal aorta with IgG purified from a patient with AAA. Collagen XI-alpha 1 (COL-11 A1) was detected after it was initially found to be overexpressed 38-fold normal in a gene chip experiment. The present searches were undertaken to explore the basis for the similarities of these two autoantigens.

Methods: Computation of the probability that similarities of protein or nucleic acid sequences are unrelated (ALL-ALL) was carried out on the Biologist's Control Panel at the National Center Biotechnology Information (NCBI) at the National Institutes Of Health.

Results: Highly significant regions of homology of both AAAP-40 and COL-11-A1 were detected to all three chains of modern fibrinogen (alpha, beta, and gamma). The chance that the two autoantigens were unrelated to each other was less than 1×10^{-27} . It is also notable that AAAP-40 has significant similarities to members of a family with known oncogenic properties (FREPs).

Conclusions: The low probability that AAAP-40 and COL-11-A1 are unrelated suggests an ancient evolutionary relationship. The similarity of AAAP-40 to oncogenic proteins may be relevant to the unexplained prevalence of neoplasia first described by E Szilagi in 1987.

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COMPARISON BETWEEN QRISK AND AGAPSS SCORES FOR CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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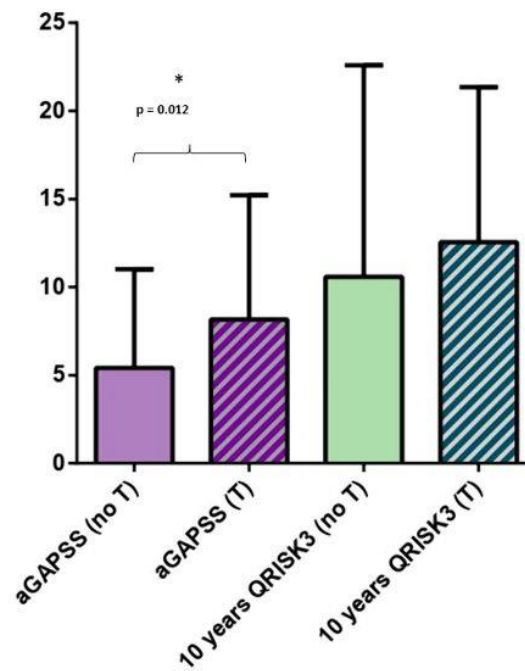
Background and Aims: Cardiovascular diseases (CVDs) represent one of the most life-threatening conditions that can affect SLE patients. Here we applied and compare the QRISK3 and the adjusted Global AntiPhospholipid Syndrome Score (aGAPSS) in a cohort of SLE patients with and without a concomitant diagnosis of APS.

Methods: 25-85 yo patients with a confirmed diagnosis of SLE and/or a diagnosis of SAPS were recruited. QRISK3 was calculated using the official online calculator (<https://qrisk.org/>). aGAPSS was calculated using the validated point values based on aPL profile and independent risk factors: aCL=5, a β 2GPI=4, LA=4, aPS/PT=3, hyperlipidemia=3, hypertension=1.

Results: The analysis included a cohort of 142 SLE patients: 34 SAPS (23.9%) and 108 SLE patients without APS (76.1%). Table 1 summarizes patients characteristics. When focusing on cerebrovascular/coronary events, we found a statistical significance with respect to aGAPSS (pt with event=10.1 \pm 6.2 vs pt without event=5.8 \pm 6.1; p=0.007), but not QRISK3. A significant association was observed between the occurrence of these events and high risk aGAPSS: p=0.03 for aGAPSS \geq 8, p=0.01 for aGAPSS \geq 9, p=0.008 for aGAPSS \geq 10. The aGAPSS but not the QRISK3 resulted to strongly correlate with the occurrence of any thrombotic event, both at the uni- and multivariate analysis (univariate: pt with event=8.17 \pm 7.1 vs pt without event=5.41 \pm 5.6; p=0.012 / multivariate: p=0.009)(Figure 1). When focusing on aPL-profile, regardless the diagnosis, we found a statistical significance only with respect to aGAPSS (aPL+ =9.6 \pm 6.3 vs aPL- = 4.1 \pm 5.1;

PATIENTS CHARACTERISTICS	
Age (m±sd)	Tot=48±12.87
	SAPS=51.61±12.82
	SLE w/o APS=46.87±12.83
Females, n (%)	Tot=120/142 (84.5%)
	SAPS=22/34 (64.7%)
	SLE w/o APS=98/198 (90.74%)
THROMBOTIC EVENTS	
Thrombotic event, n (%)	Tot=48/142 (33.8%)
	SAPS=33/48 (68.75%)
	SLE w/o APS=15/48 (31.25%)
Arterial thrombosis, n (%)	Tot=22/142 (15.49%)
	SAPS=19/22 (86.36%)
	SLE w/o APS=3/22 (13.64%)
Venous thrombosis, n (%)	Tot=32/142 (22.53%)
	SAPS=18/32 (56.25%)
	SLE w/o APS=14/32 (43.75%)
Stroke, n (%)	Tot=13/142 (9.15%)
	SAPS=13/13 (100%)
	SLE w/o APS=0/13 (0%)
TIA, n (%)	Tot=6/142 (4.22%)
	SAPS=6/6 (100%)
	SLE w/o APS=0/6 (0%)

p<0.001).



Conclusions: The aGAPSS still seems to be the most valuable tool for evaluating CVD risk in SLE patients.

PD014 / #439

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

MICROANGIOPATHY, INDEPENDENT RISK FACTOR FOR DAMAGE ACCRUAL IN ANTIPHOSPHOLIPID SYNDROME: A RETROSPECTIVE MULTI-CENTER STUDY

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Background and Aims: To assess the frequency of damage accrual (DA) in antiphospholipid syndrome (APS) and to evaluate the association with different laboratory/clinical APS subsets.

Methods: Medical records of 274 patients, 231 (84.3%) female and 43 (15.7%) males with a mean (\pm SD) age at diagnosis of 37.8 (\pm 11.5) years, followed from 1990 to 2021, were reviewed.

Results: Ninety-six (35%) had pregnancy morbidity, 140 (51.1%) thrombosis and 38 (13.9%) both thrombosis/pregnancy morbidity. Single, double or triple antiphospholipid antibodies (aPL) positivity was registered, respectively in, 82 (29.9%), 78 (28.5%) and 114 (41.6%) patients. Fifty-eight (21.2%) organ DA was recorded. This included neurological damage in 19 (32.8%), cardiac valvopathy in 4 (6.9%), chronic heart failure in 4 (6.9%), chronic renal failure in 15 (25.9%), amputation in 5 (8.6%), visual loss in 2 (3.4%), post thrombotic syndrome in 6 (10.3%), adrenal insufficiency in one (1.7%). DA rate was significantly higher in both thrombotic and thrombotic/pregnancy morbidity than pregnancy morbidity ($p < 0.0001$ (OD 40.7; 95% CI: 6.9-418.8) and $p < 0.0001$ (OD 61.9; 95% CI 10.5-659.7). Microangiopathy and both venous/arterial thrombosis were significantly associated with DA, respectively ($p < 0.0001$, OD 10.99; 95% CI 5.7-21-36) and ($p = 0.001$). DA rate was significantly higher in triple aPL than single and double aPL ($p < 0.0001$ (OD 9.6; 95% CI: 3.7-23.5) and $p < 0.0001$ (OD 4.8; 95% CI: 2.2-10.81). Microangiopathy was an independent risk factor for DA ($p = 0.001$) in multivariate analysis.

Conclusions: Our data show a higher frequency of DA in APS patients. Microangiopathy was independent risk factor for DA. These findings should be in mind when counselling APS patients and might help guide clinicians in therapeutic decision.

PD015 / #419

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

**AUTOIMMUNE SEROLOGY IN IDIOPATHIC INFLAMMATORY MYOSITIS:
EPIPHENOMENON OR CLINICAL CORRELATION?**

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Background and Aims: BACKGROUND AND AIMS: Idiopathic inflammatory myositis (IIM) defines a group of autoimmune diseases characterized by muscle inflammation, interstitial lung disease, cutaneous rash, calcinosis and malignancy. Improvements in immunoassays sensitivity and specificity led to a switch in diagnostic criteria. Muscle histology is no longer considered pivotal in IIM diagnosis. Here we investigated concordance between serological findings and final diagnosis in a cohort of patients with suspected myositis and evaluated prevalence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)-associated necrotizing myopathy.

Methods: METHODS: We prospectively collected 97 serum sample of patients attending our referral Neurological Centre in a eight-month period for suspected myopathy. Sera were tested for antinuclear antibody (ANA) (Euroimmun), myositis associated (MAAs) and myositis specific autoantibodies (MSAs) (Euroimmun Euroline), and HMGCR autoantibodies (CIA assay, INOVA). Clinical data, including muscle enzymes, electromyography (EMG) and muscle biopsy, when performed, were collected from patient electronic record.

Results: RESULTS: Of the 97 included patients, 59% presented a defined diagnosis, including connective tissue diseases (14%), neurological diseases (5%), non-necrotizing myopathy (30%), and idiopathic inflammatory necrotizing myopathy (IMNM) (8%). Serological profile was concordant with clinical and complementary instrumental findings in all patients with defined diagnosis, with the exception of one patient who had HMGCR autoantibodies positivity and a late-onset genetic mitochondrial myopathy. Prevalence of IMNM in our IIM cohort was 13%.

Conclusions: CONCLUSION: Our results showed a good correlation between serological findings and clinical manifestation, supporting the increasing role that laboratory is gaining in both IIMs and IMNM diagnosis. Anquetil et al, Autoimmun Rev. 2019 Mar; Betteridge, J Inter Med. 2016 Jul

PD016 / #429

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

INFLUENCE OF OBESITY ON THE DISEASE COURSE OF SJÖGREN'S SYNDROME

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Background and Aims: Aim of this study was to investigate how obesity influences the disease course of patients with Sjögren's syndrome (SS).

Methods: Patients were grouped according to having normal body mass index (BMI \leq 25) (n=47) or being overweight (BMI >25) (n=78). Cardiovascular risk factors, statin use, factors influencing disease course were evaluated. Immune serological parameters and ESSDAI were compared within the two groups. In a smaller cohort, serum chemerin and oxLDL levels were measured, since these adipokines are known for participating in inflammation.

Results: Although hypertension and type2 diabetes was significantly more frequent in the obese group (p=0.035 and 0.008, respectively), immunological parameters of these patients was surprisingly more beneficial than those of patients with normal BMI: ESSDAI: 2.68 \pm 3.56 vs. 5.56 \pm 5.33 (p=0.001); IgG 10.47 \pm 5.73 vs. 13.37 \pm 7.00 g/l (p=0.044); c3 1.45 \pm 0.43 vs. 1.21 \pm 0.18 g/l (p<0.001); c4 0.269 \pm 0.091 vs. 0.216 \pm 0.085 g/l (p=0.001); Rheumatoid factor positivity 46% vs 68% (p=0.017). Significantly more normal BMI patients required glucocorticoid treatment than overweight ones (p=0.018). Statin use was more frequent among obese patients (p=0.008); however, no significant difference was measured regarding cholesterol levels (p=0.189). There was no significant difference between chemerin and oxLDL levels, but there was a significant positive correlation between chemerin levels and BMI (p=0.021), c3 (p=0.0246) and logCRP (p=0.0349), whereas negative correlation was found between ESSDAI and chemerin levels (p=0.5775).

Conclusions: Immunological parameters of overweight SS patients are significantly more favorable. Anti-inflammatory effects of statins and relatively lower chemerin levels might contribute to the results. However, impact of obesity paradox cannot be ruled out either.

PD017 / #440

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

ADDED VALUE OF SYSTEMIC SCLEROSIS AND ANTI-SYNTHEASE ANTIBODY TESTING ON ILD CLASSIFICATION IN PATIENTS WITH DISTINCT RADIOLOGICAL HRCT PATTERN

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Background and Aims: Multidisciplinary team discussion (MTD) increases the diagnostic confidence in discriminating idiopathic from non-idiopathic interstitial lung disease (ILD). We aim to investigate the added value of systemic sclerosis (SSc) and anti-synthetase syndrome (ASS) antibody (Ab) testing on ILD classification in patients with a distinct HRCT pattern (e.g. usual interstitial pneumonia (UIP), organizing pneumonia (OP) and non-specific interstitial pneumonia (NSIP)).

Methods: ILD patients, diagnosed in our hospital from 02/2018-02/2021, were retrospectively included. Two consecutive MTDs, composed of a radiologist, a pneumologist and a rheumatologist were organized including 1) standard serology only, e.g.: -RF IgM and ACPA IgG -ANA testing (dsDNA IgG and ENA IgG (ANAProfile3 IgG, Euroimmun) guided by indirect immunofluorescence (IFA) -ANCA IgG (myeloperoxidase IgG and proteinase-3 IgG) guided by IFA 2) additional SSc (SCL12DIV-24) and ASS (MYOS12DIV-24) Ab results (D-tek)

Results: 116 ILD patients were included (n=67 UIP, n=33 NSIP, n=16 OP). Additional serological testing resulted in a decrease of non-idiopathic ILD classifications from 54.3% to 50.0% and increased definite systemic rheumatic disease (SRD-ILD) classification from 19.8% to 23.3% (n=2 UIP, n=1 NSIP, n=1 OP). The additional identified SRD-ILD diagnoses constituted of i)3 ASS/PM-ILD based on PL12 IgG(+++)(2x) and Th/To IgG(+++) and ii)1 SSc based on PM-Scl75 IgG(+++). Extending the serological domain of the current IPAF classification resulted in 3 new IPAF classifications.

Conclusions: Independent of the presenting HRCT pattern, serological testing for SSc ad ASS Ab added value in ILD classification. An update of the serological domain of the current IPAF classification criteria is warranted.

PD018 / #203

**E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM**

**LONG-TERM SURVIVAL IS HIGH IN SLE, BUT RISK OF DEATH IS INCREASED
COMPARED TO THE GENERAL POPULATION: DATA FROM A LARGE POPULATION-
BASED COHORT**

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Background and Aims: To provide updated information on SLE mortality rates (MRs) and standardized mortality ratios (SMRs) in a population-based study.

Methods: We analyzed all-cause mortality from January 2012 until December 2021 using the Population Registry of the Veneto Region, an administrative health database with full coverage of residents (4,900,000 people) linked with databases of healthcare copayment exemption, hospital discharges, and mortality. SLE was defined by a healthcare copayment exemption for SLE (national code 028) or any hospital diagnosis of SLE (ICD-9-CM 710.0), whichever came first. MRs were stratified by sex and age. SMRs were derived by comparing MRs of the general regional population.

Results: Between 2012 and 2021, 603 deaths among 4,283 prevalent SLE cases occurred, corresponding to a standardized MR of 18.6 (95%CI 17.0-20.2) per 1,000 person/year. Ninety out of 1,092 incident SLE patients died (8.3%), determining a MR among incident cases of 13.9 (11.1-17.0) per 10,000 person/month, with a peak within one year since diagnosis (49 deaths; MR 26.5, 18.3-37.0 per 10,000 person/month). Five- and 8-year survival was 91% and 89%, respectively. When stratifying for age, 8-year survival was 97.1% (94.5-98.5) in patients aged <60 years at diagnosis, with males having worse survival than females (90.6% vs. 98.3%, p<0.001). Overall, SMR was 2.65 (2.13-3.26). Although no deaths occurred among 192 incident patients aged <30 years old at diagnosis, SMR was as high as 5.59 (2.05-12.4) among younger patients, i.e. those 30-45 years old.

Conclusions: Although 8-year SLE survival is good, SLE mortality is still higher than expected, especially in younger patients.

PD019 / #209

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

**EPIDEMIOLOGY OF JUVENILE ONSET SLE AND PEDIATRIC SLE IN THE LAST DECADE
IN A LARGE POPULATION-BASED STUDY.**

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Background and Aims: Very limited and old data regarding the epidemiology of juvenile-onset SLE (jSLE) are available. We aimed at estimating jSLE incidence over the period 2012–2020. Moreover, we assessed point prevalence of pediatric SLE in 2020.

Methods: A retrospective population-based study was conducted using the Veneto Region Population Registry, an administrative health database recording all residents of the region (4.9 million people). Between 2012 and 2020, incident SLE cases were identified by a healthcare copayment exemption for SLE (national registry code 028) or any hospital diagnosis of SLE (ICD-9-CM 710.0), whichever came first. All SLE diagnoses in subjects <19 years old were considered. Standardized incidence rate (IR) was reported by sex. The standardized point prevalence of pediatric SLE was calculated considering all prevalent SLE cases aged <19 years in 2020.

Results: During the study period, among 1,092 incident SLE cases, 68 (6.2%) were jSLE (54 females, 79.4%). IR (95%CI) over the study period was 0.38 (0.23-0.63) x 100,000 residents in males and 1.54 (1.18-2.01) x 100,000 in females, and 0.94 overall. These rates were significantly lower than those observed in all other age groups. Incidence was 4-folds higher in females (female-to-male IR ratio: 4.09, 95% CI 2.27-7.36, p<0.0001). In 2020, 34/3,472 prevalent SLE patients were <19 years old (1%); point prevalence of pediatric SLE was 3.9 (2.6-5.2) per 100,000 residents, significantly lower than that of adults SLE (71.2, 68.8-73.5).

Conclusions: Over the last decade, jSLE incidence in Italy was 1:10,000 residents, confirming older estimates in other European countries. Pediatric SLE is a rare condition.

PD020 / #418

**E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM**

NEUROPSYCHOLOGICAL OUTCOME OF CHILDREN BORN TO WOMEN WITH SYSTEMIC SCLEROSIS: ASSESSMENT THROUGH A SELF-ADMINISTERED MULTIDISCIPLINARY QUESTIONNAIRE IN A MONOCENTRIC COHORT

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Background and Aims: To evaluate the long-term neuropsychiatric (NP) outcome of children born to SSc mothers.

Methods: 1) Creation of an ad-hoc questionnaire investigating child's neurodevelopment and administration to female SSc patients attending our Center during 2021. 2) Comparison of NP characteristics between 3 subgroups of children: A. born >10 years before-; B. born ≤10 years before-; C. born after- maternal SSc diagnosis.

Results: We collected data about 154 children born to 89 SSc women. SSc mothers declared that 7 children underwent a NP evaluation leading to a diagnosis in 3 cases: 1 cognitive delay, 1 learning disability (LD) and 1 autism spectrum disorder (ASD). At least 1 minor NP alteration was reported in 35% of children. Sleep irregularities were the most frequent disorder reported (n=15). Comparisons between the 3 subgroups of children for each NP outcome are shown in *Table 1*: overall, a higher rate of NP alterations was reported in children of group

B.

Table 1. Comparison of NP characteristics of the 154 children between 3 subgroups according to maternal diagnosis; NP alterations are divided into three main age ranges.

	A born >10 years before maternal diagnosis n=98	B born ≤10 years before SSc diagnosis n=23	C born after SSc diagnosis n=33
N° of subjects with available information for DISORDERS IN CHILDHOOD (0-5 years)	96/98	23/23	32/33
Eating disorders	6/75 (8.0)	0/19 (0.0)	2/25 (8.0)
Sleep irregularities	5/75 (6.7)*	5/19 (26.3)*	5/25 (20)
Difficulty in sphincter control	1/74 (1.4)	0/19 (0.0)	0/25 (0.0)
Motor difficulties	0/73 (0.0) [§]	2/19 (10.5) [§]	2/24 (8.3)
Difficulty in relationships	0/74 (0.0)	1/17 (5.9)	2/24 (8.3)
Difficulty in non-verbal communication skills	0/74 (0.0)	1/17 (5.9)	0/24 (0.0)
Difficulty in verbal communication skills	1/73 (1.4)	1/18 (5.6)	2/24 (8.3)
Difficulty in social integration	6/73 (8.2)	3/18 (16.7)	1/23 (4.3)
Cognitive difficulties	0/73 (0.0)	1/18 (5.6)	0/24 (0.0)
N° of subjects with available information for DISORDERS IN SCHOLAR AGE (6-11 years)	96/98	23/23	15/33
Difficulty in school lessons/homework	6/73 (8.2)	3/18 (16.7)	1/13 (7.7)
Behavioral problems during school period	3/72 (4.2)	1/18 (5.6)	2/13 (15.4)
School year repetition	10/72 (13.9)	3/19 (15.8)	0/13 (0.0)
Need for a support teacher	2/72 (2.8)	1/19 (5.3)	0/13 (0.0)
N° of subjects with available information for DISORDERS IN ADOLESCENCE (12-18 years)	96/98	18/23	8/33
Difficulty in managing anger and aggression	3/73 (4.1)	0/15 (0.0)	1/7 (14.3)
Behavioral alterations	0/73 (0.0)	0/15 (0.0)	0/7 (0.0)
Difficulty in impulse control	2/72 (2.8)	0/15 (0.0)	0/7 (0.0)
Difficulty in conduct	1/71 (1.4)	1/15 (6.7) [^]	2/7 (28.6) [^]
Mood alterations	0/71 (0.0)	1/15 (6.7)	1/7 (14.3)
Eating behavior alterations	1/73 (1.4)	0/15 (0.0)	0/7 (0.0)
Anxiety problems	1/73 (1.4)	1/14 (7.1)	0/7 (0.0)

Results are presented as number/total number (%) of answers collected for each question. Variables were compared by Chi Squared/exact Fisher test. * $p=0.03$; [§] $p=0.04$; [^] $p=0.02$; all other comparisons are not statistically significant.

Conclusions: The frequency of major NP alterations (cognitive delay, LD, ASD) in children born to SSc mothers was similar to general pediatric population. A higher frequency of minor ND disorders was observed in children born ≤10 years before maternal diagnosis, possibly suggesting an impact of maternal disease on the relationship with child in the first years of life. To confirm these self-reported data, the extension of this study will consist in a NP specialistic evaluation proposed to the offspring of SSc mothers aged ≤18 years. *GILS (Gruppo Italiano Lotta Sclerodermia)* is kindly acknowledged for supporting the study with a grant.

PD021 / #218

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

**AGREEMENT BETWEEN LLDAS AND EXPERT ASSESSMENT IN IDENTIFYING PATIENTS
IN LOW DISEASE ACTIVITY: DATA FROM A REAL-WORLD COHORT**

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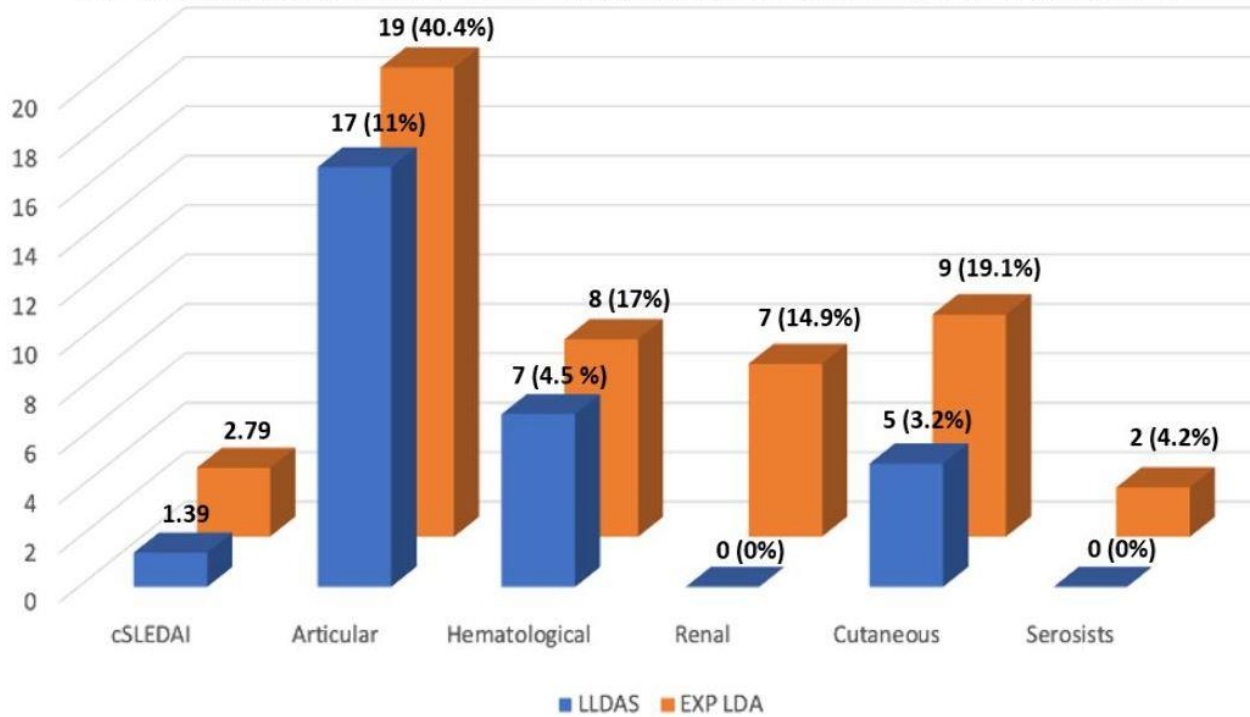
Background and Aims: Considerable overlap between LLDAS and remission exists, as 80% of LLDAS patients are also in remission in different cohorts. Our aim was to evaluate the performance of LLDAS in identifying patients in LDA, defined according to the gold standard, which is physician judgment.

Methods: We prospectively collected data of SLE patients followed-up from October 2021 to January 2022. A rheumatologist expert in SLE classified patients into three mutually exclusive states: remission, LDA, and active disease. The definitions of LLDAS (Franklyn et al. ARD 2016) and remission (DORIS definition) were also applied. Patients fulfilling the definition of LLDAS but not that of remission (LLDAS/no remission) were identified. Cohen's kappa coefficient was used to assess the agreement between the expert definition of LDA and LLDAS.

Results: We enrolled 207 SLE patients: 154 (74.4%) were in LLDAS, of which 29 (18.8%) were in LLDAS/no remission, meaning an overlap between LLDAS and remission of 81.2%. According to expert opinion, LDA was observed in 45 (21.7%) and remission in 128 (61.8%) patients, with differences in patients' manifestations captured (Figure 1). The agreement between expert opinion and LLDAS in discriminating active disease from LDA+remission was overall good (Cohen's κ 0.67). However, LLDAS failed to discriminate between patients in LDA vs. those in remission as identified by the expert (Cohen's κ -

0.02).

Clinical manifestations of LLDAS patients and patients in LDA according to the expert opinion



Conclusions: LLDAS is effective in discriminating patients with active diseases from those in LDA/remission. LLDAS failed to identify patients in LDA, as the majority of patients included in LLDAS were in remission. LLDAS definition should be implemented.

PD022 / #413

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

PREDICTORS OF MUSCULOSKELETAL RESPONSE IN SLE-PATIENTS TREATED WITH BELIMUMAB. DATA FROM A MULTICENTERED NATIONWIDE COHORT OF SLE PATIENTS TREATED WITH BELIMUMAB (BERLISS-JOINT)

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Background and Aims: Background and aims. To investigate rates and predictors of organ response to belimumab in lupus patients with musculoskeletal manifestations by using DAS-28.

Methods: Methods. We enrolled patients with SLE musculoskeletal manifestations, treated with belimumab from the BeRLiSS cohort. The outcome was evaluated by DAS28 20,50,70, defined by a decrease of at least 20%,50% and 70% at 6,12, 24, 36 and 48 months. DAS28 remission, defined by DAS28<3.2 at different time points was also evaluated. Baseline predictors were evaluated through logistic regression analysis.

Results: Results. In the analysis were included 272 patients with articular manifestations. The percentage of patients achieving the outcome at different time points were described in the figure. An association, although not significant, was found between early lupus (disease onset <2 years) and DAS28/20 ($p=0.055$) and DAS28/50 responses ($p=0.057$) at 6 months and DAS28/20 response at 12 months ($p=0.058$). Chronic active disease pattern was negatively associated with DAS28/50 at 6 months ($p=0.026$) and DAS28/20 at 24 months ($p<0.001$). Daily prednisone intake ≥ 5 mg was negatively associated with DAS28/50 at 6 months ($p=0.014$) and DAS28/50 at 12 months. DAS28 score ≥ 5.1 was associated with DAS28/50 at 6 months ($p=0.017$), DAS28/20 ($p=0.033$) and DAS28/50 ($p<0.001$) at 12 months, DAS28/50 ($p=0.006$) and DAS28/70 ($p=0.004$) at 24 months. SLEDAI at baseline was associated with DAS28/20 response at 36 months ($p=0.037$)

Conclusions: Conclusions: In belimumab-treated patients with joint manifestations, best response was found in patients with active disease, low daily prednisone intake and relapsing remitting pattern.

PD023 / #279

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

CLINICAL AND SEROLOGICAL FACTORS ASSOCIATED WITH ILD IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background and Aims: Patients with idiopathic inflammatory myopathies (IIMs) have a highly heterogeneous spectrum of serological and clinical features. They may develop interstitial lung disease (ILD), but risk factors for lung involvement remain unclear. We aimed to identify factors associated with ILD in a large multicenter prospective cohort of Caucasian patients with IIMs.

Methods: Patients (2017 EULAR/ACR criteria) enrolled in the cohort were retrospectively evaluated. Demographic, serological and clinical features were recorded at diagnosis and during follow-up. ILD was detected by chest high-resolution computed tomography or pulmonary functional tests. Univariate and multivariate analyses were performed to identify clinical and serological factors associated with ILD.

Results: ILD was detected in 125/253 (49.4%) patients. IIMs-ILD patients compared with IIMs-not ILD had significantly lower creatine phosphokinase (CPK) levels at diagnosis ($p=0.001$), higher prevalence of anti-Jo-1 (56 vs. 7, $p<0.0001$), anti-SSA/Ro (57 vs. 23, $p<0.0001$), anti-Ro52 (33 vs. 11, $p<0.0002$) and anti-MDA5 (9 vs. 1, $p=0.01$), mechanic's hands (26 vs. 4; $p<0.0001$), arthritis (38 vs. 15; $p=0.003$) and dyspnea (60 vs. 8; $p<0.0001$). Multivariate analysis identified mechanic's hands [8.56 (1.95-37.6; $p=0.004$), Raynaud's phenomenon [3.17 (1.22-7.66); $p=0.02$], anti-Jo-1 [4.48 (1.09-19.1); $p=0.04$], anti-MDA5 [10.9 (1.09-107.8); $p=0.04$], anti-Ro52 [3.90 (1.42-10.7); $p=0.008$] as independently associated with ILD. On the other hand, heliotrope rash [0.25 (0.08-0.77); $p=0.01$] was negatively associated with ILD.

Conclusions: Besides the specific autoantibodies positivity (anti-Jo1, anti-MDA5 and anti-Ro52), mechanic's hands were the strongest independent clinical manifestation associated with ILD in Caucasian IIMs patients. Our findings may help clinicians to identify patients who should be closely monitored for ILD.

PD024 / #612

E-POSTER DISCUSSION 03: CTDS 01
17-03-2023 12:55 PM - 1:55 PM

GLOMERULAR ACTIVITY AT SECOND KIDNEY BIOPSY PREDICTS OF END-STAGE KIDNEY DISEASE IN A LARGE MULTI-CENTRIC COHORT OF PATIENTS WITH ACTIVE LUPUS NEPHRITIS

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Background and Aims: To investigate second kidney biopsy as predictor of end-stage kidney disease (ESKD) in active lupus nephritis (LN).

Methods: Patients with biopsy-proven LN (ISN/RPS 2003) who underwent a second kidney biopsy between 1990 and 2018 were included. Clinical and histological findings at first and at second biopsy were analyzed with Cox proportional hazard models to predict ESKD, defined as start of kidney-replacement therapy. Survival curves were calculated with Kaplan-Meier method.

Results: Ninety-two LN patients were included. Reasons for second kidney biopsy encompassed nephritic flares (n=28, 30.4%), proteinuric flares (n=46, 50%) or lack of renal response (n=18, 19.5%). Class-switch occurred in 50.5% of cases, mainly from non-proliferative to proliferative classes. Class IV remained stable in over 50% of cases. Twenty-five patients (27.2%) developed ESKD, mostly belonging to the nephritic-flare group (17/28, 60.7%). The independent predictors of ESKD at the second biopsy were activity index (AI; HR95%CI 1.20 [1.03-1.41], p=0.022), chronicity index (CI; 1.41 [1.09-1.82], p=0.008) and 24h-proteinuria (1.22 [1.04-1.42], p=0.013). AI≥2 (log-rank p=0.03), CI>4 (log-rank p=0.001), or proteinuria≥3.5g/day (log-rank=0.009) identified thresholds for higher risk of ESKD. Glomerular activity and tubular chronicity mainly contributed to the association of AI and CI with ESKD (1.38 (1.03-1.86, p=0.032 and 1.62 (0.92-2.82), p=0.09, respectively). The presence of subendothelial deposits was independently associated with ESKD (4.8 (1.13-16.3), p=0.033). No histological or laboratory predictors emerged at first biopsy (95%CI): AI: 0.88-1.19; CI: 0.66-1.20; proteinuria 0.85-1.08.

Conclusions: High activity and chronicity at second kidney biopsy predict ESKD in patients with LN and nonresponsiveness or flaring after standard therapy. Proteinuria is confirmed as an independent kidney damaging factor. Repeated biopsy represents a useful tool for prognostic stratification.

PD025 / #448

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

EVALUATION OF CIRCULATING LEVELS OF TNF/TNFR SUPERFAMILY FACTORS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID RELATED SYNDROMES

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Background and Aims: B-cell tolerance checkpoint defects are part of the pathomechanism in humoral autoimmune disorders, such as Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS). In APS, despite the strong evidence of antibody mediated pathogenesis (aPL), specific B cell phenotype abnormalities, and the development of the disease in patients with inborn errors of immunity involving B cell ontogeny, data on the use of therapies directed toward B cells are still lacking and anticoagulation remains the corner stone of management. The aim of this study was to measure serum levels of TNF/TNFR superfamily factors which are involved in B-cell homeostasis, looking for differences among diseases.

Methods: Two hundred and twenty-seven patients [75 SLE, 62 SLE+aPL, 36 SLE+APS and 54 primary APS (PAPS)] were enrolled. The dosage was performed by high-sensitivity ELISA. Data are expressed in median (pg/ml or ng/ml for sBCMA). P values ≤ 0.05 were considered statistically significant (*).

Results: SLE patients had BAFF serum levels=316.61 vs 359.26 (SLE+aPL), 615.87* (SLE+APS), 483.31* (PAPS); APRIL=4563.53 vs 5080.33, 3142.60, 3424.06*; sBCMA=11891.15 vs 14991.55, 10372.41, 14632.88; sTACI=357.37 vs 450.51, 424.00, 486.43; sCD40L=1355.97 vs 985.42*, 1023.00, 691.96*; TWEAK=2477.49 vs 2454.60, 1683.09*, 2171.18.

Conclusions: The significant difference in circulating levels of almost all B-cell related TNF/TNFR superfamily factors between SLE and all the aPL-related conditions suggest heterogenous underlying autoimmune mechanisms. In this analysis, BAFF has emerged as a prominent marker in the condition of SLE+APS, but also in PAPS, suggesting a potential beneficial use of anti-B cell therapies in antiphospholipid related syndromes.

PD026 / #458

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

RECOMBINANT CALPROTECTIN AS A PROMISING TOOL TO HARMONIZE MRP-8/MRP-14 IMMUNOASSAYS

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Background and Aims: Calprotectin is a granulocyte-derived alarmin protein natively occurring as dimeric and tetrameric MRP-8/MRP-14 complexes. While serum calprotectin is an emerging biomarker for rheumatoid arthritis and juvenile idiopathic arthritis, fecal calprotectin has already become the gold standard for diagnostics and monitoring of inflammatory bowel diseases (IBDs). However, standardization of fecal calprotectin assays differs significantly among providers leading to varying clinical cut-offs. A suspected reason is that calprotectin's oligomeric states can generate different quantitative results yet trapping calprotectin in a distinct oligomeric state is challenging. It is therefore required to produce pure calprotectin as calibrator material with a controllable oligomeric state.

Methods: Recombinant MRP8/MRP14-fusion protein was expressed solubly in *E. coli* and the oligomeric state assessed by size-exclusion chromatography. Direct comparison to native calprotectin regarding antibody affinities were measured and its use as calibrator material in various immunoassay formats was tested.

Results: The fusion protein was purified as a calprotectin dimer mimic and could successfully be transformed into a calprotectin tetramer upon calcium addition. Affinities to monoclonal and polyclonal calprotectin antibodies are comparable to native calprotectin. Spiking of different concentrations of recombinant calprotectin showed linear correlations in ELISA and turbidimetric assays. Turbidimetric measurements of 23 human serum samples based on native and recombinant calprotectin calibrators revealed a perfect correlation (slope=1.009; R²=0.999).

Conclusions: The recombinant protein shows immunological properties comparable to native calprotectin and can be purified in large quantities in defined oligomeric states. It therefore presents a promising tool to overcome the prevalent fecal calprotectin standardization problem and prevent future standardization discrepancies for serum calprotectin.

PD027 / #216

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

CHARACTERIZATION OF EXTRACELLULAR VESICLES AND MICRORNA CARGO IN PATIENTS AFFECTED WITH IDIOPATHIC INFLAMMATORY MYOPATHIES: A LOOK TOWARDS NOVEL BIOMARKERS

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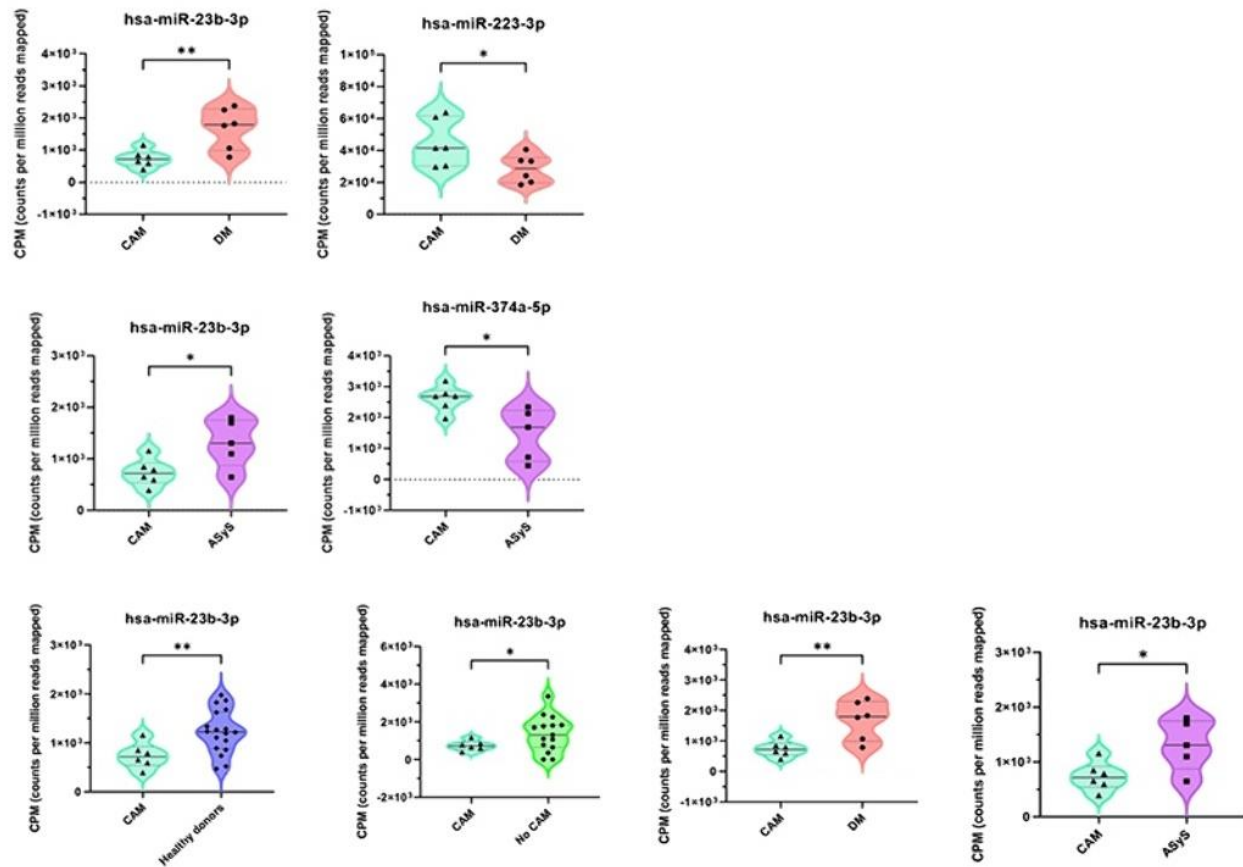
Background and Aims: Extracellular vesicles (EVs) are cell-derived nanoparticles involved in intercellular signaling and in autoimmunity. The study aims to characterize circulating EVs and miRNA cargo in patients with idiopathic inflammatory myopathies (IIM) and healthy donors (HDs) to explore their potential function as biomarkers.

Methods: EVs were isolated from platelet-free plasma of IIM patients and HDs through size exclusion chromatography and ultrafiltration. EVs were quantified by nanoparticles tracking analysis (NTA) and EVs-microRNA cargo investigated through Next-Generation Sequencing (NGS).

Results: NTA measurements reported higher mean EVs concentration in IIM patients (n=58) versus HDs (n=60) ($1,75 \times 10^{10} \pm 1,35 \times 10^{10}$ SD [EVs/mL] vs $1,34 \times 10^{10} \pm 7,35 \times 10^9$; $p=0,0461$). After NGS analysis 10 miRNA displayed significant different expression levels ($p<0.05$) between IIM patients (n=21) and HDs (n=21): 6 were upregulated (hsa-miR-451a, hsa-miR-15a-5p, hsa-miR-486-5p, hsa-miR-222-3p, hsa-miR-32-5p, hsa-miR-185-5p) and 4 downregulated (hsa-let-7b-5p, hsa-let-7a-5p, hsa-let-7e-5p, hsa-let-7f-5p) in the patient's group. Among IIM subtypes, miR-23b-3p was significantly higher expressed in dermatomyositis (DM) group (n=6) versus CAM (n=6) ($1.68 \times 10^3 \pm 638.4$ vs 737.2 ± 260 [Counts per million, CPM]; $p=0.0073$) while miR-223-3p had opposite expression profile in the two groups ($2.858 \times 10^4 \pm 8.758 \times 10^3$ vs $4.477 \times 10^4 \pm 1.463 \times 10^3$ [CPM]; $p=0.0423$). miR-23b-3p was higher in antisynthetase (ASyS) (n=7) versus CAM ($1.311 \times 10^3 \pm 467.3$ vs 737.2 ± 260 [CPM]; $p=0.0295$) while miR-374a-5p displayed opposite expression profile among these two IIM subtypes ($2.621 \times 10^3 \pm 406.8$ vs $1.472 \times 10^3 \pm 845.7$ [CPM]; $p=0.0159$). miR-23b-3p resulted downregulated in CAM compared to HDs ($p<0.001$), DM ($p<0.001$) and ASyS ($p<0.05$) (Figure

1).

Figure 1. Different miRNA expression among different IIM subtypes



Conclusions: The differential expression of EVs load and miRNA cargo suggests a possible role for EVs in IIM pathogenesis. Peculiar miRNA profiles may help defining and targeting different IIM subtypes.

PD028 / #573

E-POSTER DISCUSSION 04: BIOMARKERS
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A RANDOMIZED CONTROLLED PROSPECTIVE SINGLE-CENTER FEASIBILITY STUDY OF RHEOPHERESIS FOR RAYNAUD'S SYNDROME AND DIGITAL ULCERS IN SYSTEMIC SCLEROSIS (RHEACT) - PRESENTATION OF FIRST INTERIM RESULTS

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Background and Aims: Raynaud's phenomenon (RP) and digital ulcers (DU) are frequent manifestations of Systemic Sclerosis (SSc). There are very few available approved drugs with varying efficacy. Rheopheresis (RheoP) is an extracorporeal apheresis technique used to treat microcirculatory disorders by improving blood viscosity. We performed a randomized controlled prospective single-center study using RheoP for RP and DU and present the first interim results.

Methods: "A randomized controlled prospective single-center feasibility study of Rheopheresis for Raynaud's syndrome and Digital Ulcers in Systemic Sclerosis (RHEACT)." RHEACT aims to investigate the efficacy of RheoP on the Raynaud Condition Score (RCS) as the primary outcome measure after 16 weeks from baseline. A planned number of 30 patients will be randomized in a 1:1:1 ratio to one of two RheoP treatment groups or assigned to the standard of care (SoC) control group (intravenous iloprost).

Results: We here report the results of the first seven patients. The patient assigned to the RheoP1 group had a baseline Raynaud Condition Score (RCS) of 8, which improved to 0 after 16 weeks (the primary endpoint). The two patients randomized to the RheoP2 had a baseline RCS of 8 and 6, respectively, which improved to 4 and stayed unchanged at 6 in the second patient. The four patients assigned to SoC had only minimal improvement. Furthermore, DU completely healed in the patient with DU at baseline with RheoP therapy and avoided amputation in one patient.

Conclusions: RheoP improved the RCS and DU better than SoC (Iloprost) treatment alone and avoided amputation in one patient.

PD029 / #587

E-POSTER DISCUSSION 04: BIOMARKERS
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PAIN AND FATIGUE IN FIBROMYALGIA AND ME/CFS – LESSONS FROM A NOVEL IN VIVO HUMAN EXPERIMENTAL MODEL

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Background and Aims: Background: Fibromyalgia and ME/CFS are multifaceted conditions with overlapping symptoms; the pathophysiological mechanisms are complex. It remains unclear whether dysregulated inflammation, induced either by an exogenous stimulus (eg a virus or other stressor), or autoimmunity, is of prime importance. Aims: 1. To determine in a novel human model the effects of an *in vivo* inflammatory challenge in the induction of pain and fatigue in fibromyalgia and ME/CFS compared to controls 2. Explore potential mediators and moderators involved

Methods: We studied 48 patients with Fibromyalgia and/ or ME/CFS and 22 matched controls. All underwent a placebo-controlled inflammatory challenge. Subjective pain and fatigue were assessed after saline injection and typhoid vaccination (VAS). Linear regression models were used to explore predictors. In mediation analyses predictor variable was group membership (patient or control), outcome variable was change in 1) pain and 2) fatigue induced by challenge and mediators/moderators including change in IL-6 induced by inflammatory challenge.

Results: Being a patient rather than control significantly predicted inflammation-induced fatigue (B=14.89 (95%CI 3.29-26.50), p=0.013) and pain (B=12.88 (95%CI 0.65-25.10), p=0.039) adjusting for placebo-induced levels. Induced pain was independently predicted by placebo controlled level of IL-6 induced by inflammatory challenge (B=23.44 (95%CI 5.15-41.72), p=0.013) as was induced fatigue (B=10.63 (95%CI 2.84-18.41), p=0.008).

Conclusions: In this first human study to evaluate directly the effect of an exogenous inflammatory challenge (typhoid vaccination) in a group of Fibromyalgia and ME/CFS patients, IL-6 was shown to be a critical mediator. This work strongly supports the hypothesis that inflammation is key to the pathophysiology of ME/CFS.

PD030 / #288

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

ESTIMATED FREQUENCY OF MYOSITIS AUTOANTIBODIES DETECTED BY MULTIPARAMETRIC IMMUNOASSAYS IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background and Aims: Background. The usefulness of myositis autoantibodies (MSA/MAA) profiling for the assessment of idiopathic inflammatory myopathies (IIM) is widely recognized. **Objective.** To estimate the frequency of MSA/MAA by whole-spectrum line immunoassay (LIA) in a multi-center cohort of patients with IIM.

Methods: Methods. We tested the sera from 411 patients affected with definite IIM, according to 2017 EULAR/ACR criteria, including 142 polymyositis (PM), 147 dermatomyositis (DM), 19 cancer-associated myositis (CAM), and 103 overlap myositis (OM). MSA/MAA were determined by LIA (Euroimmun, Germany), anti-HMGCR by ELISA (Werfen Autoimmunity, US) in 157/411 IIM sera. The results were compared with particle-based multi-analyte technology (PMAT) (Werfen, research use only) in 91/411 sera. Statistics was performed by Fisher's exact test.

Results: Results. MSA and/or MAA were found in 307/411 (75%) IIM patients: Jo-1+ 82/411 (20%), PL-7+ 12/411 (3%), PL-12+ 16/411 (4%), EJ+ 4/411 (1%), OJ+ 3/411 (0.7%), Mi-2+ 33/411 (8%), SRP+ 38/411 (9%), TIF1-g+ 23/411 (5.6%), MDA5+ 19/411 (4.6%), NXP2+ 6/411 (1.4%), SAE1+ 7/411 (1.7%), Ku+ 17/411 (4%), PM/Sci 75/100+ 35/411 (8.5%), HMGCR+ 8/157 (5%), and Ro52+ 105/411 (25.5%). A concordance between LIA, ELISA and PMAT was found in 75/91 (82%) sera. Some MSA were associated with different IIM forms: Jo-1 with PM and OM ($p<0.001$), PL-12 with OM ($p<0.001$), Mi-2 with DM ($p<0.001$), SRP with PM ($p<0.001$), TIF-1g with DM and CAM ($p<0.001$), MDA5 with DM ($p<0.001$), Ku and PM/Sci 75/100 with OM ($p=0.017$, $p<0.001$).

Conclusions: Conclusions. Due to MSA mutual exclusivity, extended MSA/MAA profiling is strictly effective for targeted clinical-serologic approach to the diagnosis of IIM.

PD031 / #452

E-POSTER DISCUSSION 04: BIOMARKERS
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T CELL ACTIVATION IN WOMEN WITH RECURRENT PREGNANCY LOSS AND IMMUNOLOGICAL ABNORMALITIES

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Background and Aims: A subgroup of women with unexplained recurrent pregnancy loss (RPL) disclose distinct immunological abnormalities. The potential role of this immunologic profile in the pathogenesis of RPL is not well defined. The immunological evaluation of RPL is necessary to identify potential causes of pregnancy loss but also to identify women that could require a more careful clinical follow-up. It can also give a clue as to which therapies should be evaluated.

Methods: We aimed to evaluate cellular immunity characteristics in women with an immunological profile detected in routine protocolized evaluations at the time of assessment for RPL. The immune profile was defined as having 2 or more immunological abnormalities including positive autoantibodies, low complement factors and higher NK cell counts. All patients have had 2 or more pregnancy losses. Exclusion criteria was the presence of genetic, anatomic, hormonal or thrombophilia factors associated with RPL. Controls were women with RPL without the immune profile and women without previous history of pregnancy. We evaluated the immunophenotypic activation status of CD4+ and CD8+ T-cells in peripheral blood by flow cytometry.

Results: We evaluated 10 women with RPL who had an immunological profile, 26 women with recurrent pregnancy loss without the immune profile and 52 women who have never been pregnant. Women with the immunological profile were found to have significantly higher percentages of T-cell activation and central memory CD4 status markers: CD4+DR+, CD8+DR+ and CD4+CD45RA-CCR7+ percentages.

Conclusions: Immunophenotypic abnormalities of T-cells could be associated with the pathogenesis of recurrent pregnancy loss among women with immunological abnormalities.

PD032 / #250

E-POSTER DISCUSSION 04: BIOMARKERS
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INTERLEUKIN-10 AND INTERFERON- γ IN MULTIPLE SCLEROSIS

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Background and Aims: IL-10-producing B cells (B10 cells) and IFN- γ producing CD3⁺ T cells (CD3⁺-IFN- γ cells) are impaired in autoimmune diseases, including MS. However, there is limited data regarding the status of these cells naive MS patients. Our aim was to investigate the functional alterations in B-10 and CD3⁺-IFN- γ cells in naive MS patients.

Methods: PBMCs were obtained from 14 naive MS, 16 RRMS patients and 17 healthy controls (HC). The expression of CD19 on B cells and of CD3 on T cells was examined by flow cytometry. IL-10 and IFN- γ expression was assessed by measuring intracellular IL-10 and IFN- γ expression.

Results: B10 cells were significantly decreased in MS patients compared to HC ($4\% \pm 3.8\%$ vs $8.8\% \pm 3.4\%$, $p=0.001$). However, in naive MS patients, B10 cells were comparable to HC ($5.9\% \pm 4.5\%$ vs $8.8\% \pm 3.4\%$, $p=0.186$). Amongst the naive MS patients, B10 cells were as high as 12.6% of total B cell population (range: 0.7%-12.6%, median: 4.4), with 5/13 naive MS patients exhibiting higher percentages of B10 cells than the mean percentage in HC. On the other hand, CD3⁺-IFN- γ cells were significantly decreased in MS patients compared to HC (MS: $13.1\% \pm 5.3\%$; naive MS: $12.8\% \pm 6.3\%$; HC: $19.7\% \pm 4.4\%$; MS vs HC, $p=0.005$; naive vs HC, $p=0.015$). B10 cells and CD3⁺-IFN- γ cells numerical status did not correlate. These population did not correlate with MS clinical characteristics, including the EDSS, disease duration, age at onset, progression index and relapses.

Conclusions: Contrary to our expectation, B10 cells were not universally impaired in patients with MS and did not correlate with CD3⁺-IFN- γ cells.

PD033 / #109

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

DEVELOPMENT AND EVALUATION OF I-TRACKER TOCILIZUMAB AND I-TRACKER ANTI-TOCILIZUMAB KITS: FAST AND INNOVATIVE CHEMILUMINESCENT ASSAYS FOR THE MONITORING OF PATIENTS TREATED WITH TOCILIZUMAB

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Background and Aims: Tocilizumab, an IL-6 receptor blocker, is a drug widely used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. Theradiag has just developed innovative assays for the quantification of Tocilizumab and Anti-Tocilizumab antibodies on the fully automated random access i-Track¹⁰ chemiluminescent analyzer.

Methods: Analytical performances were assessed with spiked and clinical human serum samples. Tocilizumab from serum samples was captured with magnetic microparticles coupled to IL-6 receptor and detected with polyclonal antibodies directed against Tocilizumab and conjugated to acridinium ester. Anti-Tocilizumab antibodies were captured with magnetic microparticles coupled to Tocilizumab and detected with the use of Tocilizumab conjugated to acridinium ester. Light emission was linked to the quantity of Tocilizumab, or anti-Tocilizumab antibodies present in the sample.

Results: Tocilizumab measurement showed high accuracy (recovery was between 80% and 120%). High precision was reached for both assays (CV were below 20%) and no interference was seen with biologic agents (rheumatoid factors, bilirubin...). The dynamic ranges of the assays were 0.5 to 60 µg/mL for Tocilizumab and 10 to 2000 ng/mL for anti-Tocilizumab antibodies. i-Tracker results were compared to respective ELISA based Lisa-Tracker assays and showed excellent correlations ($R^2 = >0.90$ for Tocilizumab assay and $R > 0.80$ for Anti-Tocilizumab assay).

Conclusions: i-Tracker kits are innovative assays which exhibit fast (time to results < 40min), accurate and reproducible results. i-Tracker kits are valuable tools for the monitoring of patients treated with Tocilizumab.

PD034 / #359

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

DEVELOPMENT OF TCR TREGS FOR GOODPASTURE'S DISEASE

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Background and Aims: Critical in maintaining self-tolerance and preventing autoimmunity are T regulatory cells (Tregs), a subset of suppressor T cells that suppress self-reactivity and autoimmunity. The T cell receptor (TCR) on T cells, including Tregs, is an antigen-specific receptor that can activate T cells on presentation by its ligand, peptide-human leukocyte antigen (HLA). TCRs specific for autoantigens act as a double-edged sword in autoimmune disease. If present on T effector cells, antigen-specific TCRs exacerbate and drive disease pathology. If present on Tregs, however, they act as potent suppressors of autoimmunity. We used a model autoimmune disease, Goodpasture's (GP), to show that previously published TCRs from GP patient's T effector cells can be expressed in Tregs (GP-TCR Treg) and produce effector functions.

Methods: GP-TCR Tregs were bioengineered through lentiviral transduction. Technical improvements to the native GP-TCR sequence constant region were made to enhance correct TCR pairing and expression. *In vitro* activation and suppression assays were undertaken to assess functional responses.

Results: GP-TCR was transduced onto human Tregs at 50% efficiency. The expression of GP-TCR remained stable long term in 40-day culture as did the Treg phenotype (>90% CD4⁺CD25⁺CD127^{lo/-}). GP-TCR was shown to be functionally active in the presence of its cognate antigen presented by HLA-DR15 by activation markers and suppressive capacity.

Conclusions: We show an improved system for transducing autoantigen-specific TCRs onto Tregs. GP-TCR Tregs offer a potential cell-based therapeutic for Goodpasture's disease as well as setting the premise for TCR Tregs in other autoimmune diseases.

PD035 / #376

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

FERTILITY ISSUES IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background and Aims: Systemic lupus erythematosus (SLE) affects women of childbearing age, causing concerns over disease outcome and treatment safety. The aim of this study is to assess the occurrence of complications during pregnancy in SLE and the disease impact on family planning.

Methods: A questionnaire-based study with live and online distribution to a SLE cohort including gynaecological, obstetrical and rheumatological history, breastfeeding and pregnancy outcomes.

Results: Final analysis included 70 female SLE patients, median age of 36 and a median number of births of 2. 59% were mothers before their rheumatic diagnosis. Almost 40% did not use any method of birth control, while the rest mentioned oral contraceptive pills, condoms or intrauterine devices. 44% of the subjects experienced disease flare during pregnancy. A third confirmed complications like hypertension, preeclampsia or gestational diabetes. There were no cases of neonatal lupus, however 32 miscarriages in the first trimester of which 38% attributed to secondary antiphospholipid syndrome. The most frequently used drugs were hydroxychloroquine, prednisone and non-steroid anti-inflammatory drugs. 58% of patients have an annual gynaecological check-up. A half (52%) of patients wish to conceive, but the majority (59%) fear the treatment and both maternal and fetal long and short-term evolution.

Conclusions: Uncertainty regarding clinical evolution mainly influences the decision of conception in SLE patients. Fetal complications may represent another concern. Pursuing pregnancy in lupus patients requires rigorous planning and a multidisciplinary approach in order to diminish associated risks for both mother and child.

PD036 / #561

E-POSTER DISCUSSION 04: BIOMARKERS
17-03-2023 12:55 PM - 1:55 PM

GENDER DIFFERENCES IN DISEASE SEVERITY AMONG PATIENTS WITH RHEUMATOID ARTHRITIS. A RETROSPECTIVE COHORT STUDY FROM A SINGLE CENTER.

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Background and Aims: Rheumatoid Arthritis (RA), a prototypical inflammatory disease, often results in comorbidities from chronic inflammation as well as from exposure to medications. Identification of gender-based differences in comorbidities and disease severity may assist health practitioners in providing optimum care. The aim of this study, was to determine the effect of gender on RA comorbidities and disease severity, which utilized hospital collected data from a large RA patients' cohort during a 15-year period.

Methods: In the current cohort 612 patients with RA were included, 57% of which were female. Patients were assessed in a tertiary university hospital in Greece between 2006 and 2021 and had a diagnosis of RA according to ACR and EULAR criteria. During this period all comorbidities were recorded as well as patients' disease activity.

Results: Male patients had significantly greater disease severity compared with female patients as well as they tend to develop more likely cardiovascular complications. On the other hand, female patients had more autoimmune diagnoses other than RA (such as Sjögren's syndrome) compared to male patients. Additionally, female patients had significantly greater odds of presenting urinary tract infections, hypothyroidism, depression, osteoporosis and fibromyalgia.

Conclusions: Although the prevalence of RA among males is less common, male patients have the potential for greater disease severity and are more likely to suffer from cardiovascular disease. However, differences in disease severity should be further evaluated, but with an index that includes the main comorbidities of the disease.

PD037 / #190

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS: SEX DIFFERENCES

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Background and Aims: The goal is to evaluate and compare the traditional cardiovascular risk factors (TRF), carotid plaques and cardiovascular events (CVE) in both males and females with SLE.

Methods: This study included 227pts: 69%(n=156) females, aged 35,4±0,8years and 31%(n=71) males, aged 36,1±1,3years with SLE. Carotid plaques were assessed by ultrasound(US). In accordance with the NICE guidelines high-risk was considered for Framingham scores ≥10%.

Results: There were no gender differences in: age, disease duration(133,7±9,6months in females and 131,4±12,9months in males), SLEDAI-2Kscore(9,51±0,59 and 9,15±0,98), mean SDI score(1,91±0,16 and 1,85±0,2) and steroid use duration. The cumulative prednisone dose was lower in women(39,1±3,4 and 80,1±6,6grams, p<0,001). SLEmen compared to SLEwomen had a higher incidence of current smoking (61% and 21%,p<0,001), higher systolic BP(135±2,6 and 126±1,6 mmHg,p<0,001) and diastolic BP(90±1,7 and 79,9±1,1 mmHg,p<0,001), CV risk(13,2±1,5 and 5,1±0,07%,p<0,001). Following carotid US assessment, atherosclerotic plaques (IMT≥1,5 mm) occurred in 41% of SLEmen versus 16% of SLEwomen,p<0,001.SLE men had hazard ratio (HR) of carotid plaques of 2,63(95%CI 1,66-4,19). Clinical manifestations of atherosclerosis (CVE) were reported in 31% of SLEmen vs 13% of SLEwomen,p<0,001. Out of them CAD was in 21% vs 10%,p<0,05, myocardial infarction (MI)-in 6% vs 5%,p>0,05, stroke – 10% vs 5%,p>0,05. SLEmen had HR of CVE of 2,42(95%CI 1,41-4,13), of CAD – 2,2 (95%CI 1,14-4,24).

Conclusions: Framingham risk score, the frequency of CVE (CAD, MI) and carotid plaques is higher in SLE men than in women. Male sex is associated with a greater frequency of smoking, blood pressure levels and steroid cumulative dose in SLE; these risk factors should be corrected first.

PD038 / #254

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

EVALUATION OF LFA-REAL OUTCOME MEASURES IN THE ASSESSMENT OF LUPUS DISEASE ACTIVITY

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Background and Aims: We aimed to compare recently developed lupus disease activity measures Lupus Foundation of America Rapid Evaluation of Activity in Lupus clinician reported outcome (LFA-REAL ClinRO) and patient reported outcome (LFA-REAL PRO) with traditional systemic lupus erythematosus (SLE) activity measures.

Methods: We performed a cross-sectional analysis of disease activity in SLE patients using Physician Global Assessment (PGA, range 0-100), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), LFA-REAL ClinRO (range 0-1400) and LFA-REAL PRO (range 0-1200).

Results: The study included 104 SLE patients, mostly women (91.4%), with a mean age of 45.5 (± 12.8) years. The median SLEDAI-2K score was 4 (0-29), clinical SLEDAI-2K was 3 (0-25), PGA was 28 (0-78), LFA-REAL ClinRO was 41.5 (0-186) and LFA-REAL PRO was 197.5 (0-599). There was a highly significant strong correlation between LFA-REAL ClinRO and following outcome measures: PGA ($r=0.947$, $p<0.01$), SLEDAI-2K ($r=0.836$, $p<0.01$) and clinical SLEDAI-2K ($r=0.879$, $p<0.01$). The LFA-REAL PRO showed significant moderate correlation with PGA ($r=0.357$, $p<0.01$), SLEDAI-2K ($r=0.323$, $p=0.001$) and clinical SLEDAI-2K ($r=0.377$, $p<0.01$). We also found significant moderate correlation between LFA-REAL ClinRO and LFA-REAL PRO ($r=0.402$, $p<0.01$). The LFA-REAL ClinRO had moderate correlation with immunological parameters: anti-ds-DNA ($r=0.339$, $p<0.01$), C3 ($r=-0.406$, $p<0.01$) and C4 ($r=-0.420$, $p<0.01$). On the other hand, LFA-REAL PRO had no correlation with the immunological markers of SLE activity: anti-ds-DNA ($p=0.979$), C3 ($p=0.945$) and C4 ($p=0.881$).

Conclusions: LFA-REAL ClinRO and LFA-REAL PRO outcome measures show a strong correlation with PGA and SLEDAI-2K, as well as moderate mutual correlation.

PD039 / #329

E-POSTER DISCUSSION 05: CTDS 02
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A SERIES OF INFLAMMATORY IDIOPATHIC MYOPATHIES (IIM) PATIENTS TREATED WITH SUBCUTANEOUS IMMUNOGLOBULIN (20% SCIG)

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Background and Aims: Idiopathic inflammatory myopathies (IIM) are a group of rare autoimmune diseases with systemic involvement and severe complications. First-line therapy is steroid followed by immunosuppressants. Immunomodulatory effect of intravenous immunoglobulin (IVIg) is highly effective in the management of IIM, as confirmed by multiple evidence. Our referral centre was the first to use subcutaneous immunoglobulins (20%SCIg) in patients with DM/PM. Here we present data relating to long-term follow-up of these patients.

Methods: 30 patients with DM or PM, diagnosed according to the Bohan and Peter criteria and confirmed by EULAR / ACR 2017 were included in this study. All patients had received at least one round of 20% SCIg treatment (Hizetra®, CSL Behring GmbH, Marburg, Germany, at weekly dose of 0.1-0.2 g / kg) with a follow-up period of at least one year. The median follow-up was 12-48 months and we evaluated clinical and laboratory parameters of the disease: serum CK levels, skin involvement, muscle strength assessed by Manual Muscle Test 8 (MMT8), Myositis Intention to Treat Activity Index (MITAX), Myositis damage index (MDI), HealthAssessment Questionnaire related to physical disability (HAQ-DI), Dysphagia Outcome and Severity Scale (DOSS). All parameters were evaluated before and after 20% SCIg therapy.

Results: A significant improvement was observed in creatine kinase levels, skin manifestations, MMT8 score, disease activity (MITAX), disability (HAQ-DI), and dysphagia. Side effects of 20% SCIg therapy were limited to mild local self-healing skin reactions.

Conclusions: Despite the restricted sample size, the efficacy and safety of 20% SCIg therapy in patients with DM and PM is evident in long-term follow-up.

PD040 / #296

E-POSTER DISCUSSION 05: CTDS 02
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**INTERSTITIAL LUNG DISEASE IN IDIOPATHIC INFLAMMATORY MYOPATHIES (IIMS-ILD):
ASSOCIATION BETWEEN RADIOLOGICAL PATTERN AND CLINICAL PHENOTYPE**

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Background and Aims: Interstitial lung disease (ILD) is the most frequent organ involvement in patients with idiopathic inflammatory myopathies (IIMs), however little is known on the correlation between radiologic features and the clinical phenotype of IIMs. We aimed to ascertain whether high-resolution computed tomography (HRCT) features differ among IIMs patients according to different phenotypes.

Methods: Patients affected with IIMs (polymyositis - PM; dermatomyositis - DM; anti-synthetase Syndrome - ASS) from our multicentre prospective cohort were retrospectively considered. IIMs-ILD patients with available HRCT at ILD diagnosis were included. The following prevalent radiological pattern were evaluated by expert radiologists: ground-glass-opacities, GGO; fibrotic changes, FC; consolidation, C. Clinical, functional, and serological data were collected.

Results: The prevalent CT pattern was GGO (n=39;50%), characterized by preserved lung volume at presentation compared with the other two groups (FVC%pred.=89% GGO vs. 74% FC vs. 72% C; p=0.003). Among the C group (n=17; 22%), ILD onset often preceded the diagnosis of IIMs (median 0, range [-1-24] GGO vs. 0 [-5-13] FC vs. 0 [-8-0] C years; p=0.03), with significantly increased creatine phosphokinase (252 GGO vs. 121 FC vs. 1380 C U/L; p=0.04) and lower manual muscular test (p=0.005). Interestingly, twenty two (28%) patients presented FC at ILD onset. The distribution of HRCT patterns did not differ among PM, DM and ASS.

Conclusions: GGO was the predominant HRCT pattern and associated with normal lung volume. Over 25% of our IIMs-ILD population had fibrotic changes at ILD onset. Consolidation requires particular attention as it is associated with muscle injury and often precedes the diagnosis of IIMs.

PD041 / #616

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

THE EFFECT OF DISEASE AGGRESSIVENESS AND ACTIVITY ON THE DEVELOPMENT OF FATIGUE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background and Aims: Fatigue is very common in rheumatoid arthritis (RA) patients. It affects around 40–80% of these patients. Fatigue is one of the most commonly reported symptoms, associated with pain, depression and anxiety, and affecting function, work and quality of life. This study aimed to determine the development of fatigue depending on proinflammatory cytokines in RA patients.

Methods: Overall 30 RA patients: 23 females (76.7%), 7 males (23.2%) with average age 59.5 ± 11.2 (ranging from 39 to 79) were included in the study, interviewed using adapted interview questions created by Minnock et.al. (2016). The level of the proinflammatory cytokines TNF- α , IFN-g, IL-2, IL-6, IL-17 and IL-23 was determined by ELISA test.

Results: Based on the results of the survey, RA patients were divided into two groups - with and without fatigue. In RA patients with fatigue an increase in the level of IL-6 correlate with an increase in the level of IFN-g, IL-17 and TNF- α , respectively, as well as an increase in the level of IL-21 and a decrease in the level of TNF- α . In the non-fatigue group, positive correlation between an increase in the level of IL-21 and an increase in the level of IFN-g, IL-17 and IL-2, as well as between an increase in the level of TNF- α and an increase in the level of IL-2, IL-21 and IL-23 was observed.

Conclusions: Study data suggest that only IL-6 do not significantly affect the development of fatigue in RA patients.

PD042 / #507

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

IDENTIFYING POTENTIAL CARE GAPS IN THE DIAGNOSIS OF ANTIPHOSPHOLIPID SYNDROME – A UNITED STATES REAL-WORLD DATA EVALUATION

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Background and Aims: An Antiphospholipid syndrome (APS) diagnosis requires the presence of at least one clinical criterion and one laboratory test criterion, confirmed after 12 weeks. Missed or delayed identification of APS introduces avoidable patient risk.

Methods: A retrospective cohort study was designed with 63 APS related clinical and laboratory variables, collected from 01/01/2011 to 12/31/2019. Follow-up data was collected for one-year. Exclusion criteria were defined as patients < 18yr and > 75yr. Clinician and patient demographics were also collected. Testing patterns within this APS suspected cohort were evaluated to better understand whether potential diagnostic care gaps exist within initial and confirmatory APS testing.

Results: 16,679 patients received one or more APS tests, of which 1,372 also had an associated ICD code. Within this APS tested group, 22% (n=3,665) received the full panel of recommended tests. Of these patients, 68% received no follow up testing and 5% received the complete battery of follow up tests. 27% of these patients received an incomplete battery of follow up confirmatory tests.

Conclusions: Care gaps exist in APS diagnosis. Most patients in our cohort, suspected of APS, did not receive the full scope of criteria recommended tests. Of those who did, nearly 1/3 received incomplete follow up testing, required to confirm an APS diagnosis. This diagnostic care gap places patients at risk for future complications related to potential missed APS diagnosis. Downstream risk/ burden can be mitigated through the implementation of appropriate profiles and education through the clinical laboratory.

PD043 / #613

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

DIETARY GLUTEN AS POSSIBLE DRIVER IN MYOSITIS SUBSETS: CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGICAL INTERCONNECTIONS BETWEEN IDIOPATHIC INFLAMMATORY MYOPATHIES AND THE AUTOIMMUNE GLUTEN-RELATED DISORDERS

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Background and Aims: Background: Idiopathic inflammatory myopathies (IIM) and concomitant celiac disease (CeD) are reported at 4.5-6%. A systematic review of all such published cases reported gastrointestinal symptoms in only 1/3; CeD-related antibodies were infrequent. Myositis disease activity decreased on gluten-free diet (GFD) in 58%, including three inclusion body myositis patients; 29% remained in IIM remission with GFD as sole therapy. In 2/4 patients deteriorating on GFD, control duodenal biopsies indicated non-adherence. Myositis symptoms debuted while exposed to dietary gluten in all except one case. **Aim:** Explore a possible pathophysiological connection between IIMs and CeD.

Methods: Methods: Extensive non-systematic literature searches. Relevant articles and references gave direction for succeeding searches.

Results: Results: IIMs share common pathophysiological traits with autoimmune gluten-related disorders (GRDs) CeD, dermatitis herpetiformis (DH), and gluten ataxia (GA), conditions characterized by generation of autoantibodies, tissue damage, and common HLA-DQ2.5/DQ8 haplotypes. IIM and GRDs display organ histopathology parallels including presence of transglutaminases. Disease-relevant CD4+ T cells of a highly specific phenotype is reported in CeD and connective tissue disease. In CeD and IIM, expanded T cell clones with identical phenotypes and TCR CDR3 β motifs can persist for years in blood and affected organ tissue, pointing to the presence of a continuous, antigen-driven T cell response. Clonally expanded CD8+ T cells are found in blood and muscle in IIM, versus CD4+ T cells in affected gut tissue in CeD.

Conclusions: Conclusion: Pathophysiological similarities between IIM subsets and GRDs warrant research into the possibility of exposure to gluten or gluten-related substances as possible driver in IIM subsets.

PD044 / #125

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

PREVALENCE OF AUTOANTIBODIES DIRECTED AGAINST SECONDARY NECROTIC CELLS IN SLE PATIENTS

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Background and Aims: Systemic lupus erythematosus (SLE) is characterized by autoantibodies against nuclear autoantigens. During apoptosis antigens are congregated and modified increasing the potential of autoimmune reactions. It was shown that a novel diagnostic test which employs apoptotically modified nuclear remnants, Secondary NEcrotic Cells (SNEC), allowed sensitive detection of pathologically relevant autoantibodies in serum of patients with lupus disease. Within this study, we aimed to validate technical and clinical performance of this assay with an independent patient cohort.

Methods: For the validation study, an indirect enzyme-linked immunosorbent assay (ELISA) detecting autoantibodies directed against SNEC was used to measure serum samples from 115 SLE patients, 50 healthy donors and 286 disease controls. To compare the results with classical, serological biomarkers, the samples were measured using the EliA™ technology (Thermo Fisher Scientific, Phadia AB, Sweden).

Results: The technical evaluation demonstrates a high stability and reproducibility of the ELISA using secondary necrotic cells as immobilized antigens. The measurement of an SLE patient cohort revealed a comparable clinical performance as shown by Biermann et al. with a sensitivity and specificity of 56% and 98%, respectively. When comparing the results with established, serological biomarkers, the measurement of anti-SNEC antibodies results in an added value of approx. 27% sensitivity in the seronegative patient group.

Conclusions: This study validated the previous results regarding technical and clinical performance of the SNEC-ELISA. Comparison to established serological markers reveals an added sensitivity of 27% among seronegative samples indicating that SNEC-ELISA includes to date unidentified additional autoantigens and therefore allows more accurate classification of suspected SLE patients.

PD045 / #8

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

ACTEOSIDE ATTENUATED REGULATORY B CELL FUNCTION IN PRIMARY SJOGREN'S SYNDROME

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Background and Aims: In this study, we aim to first identify the IL-10-producing regulatory B (Breg) cell function in patients with primary Sjogren's syndrome (pSS) and perform drug screening using our previously established mouse model with experimental Sjogren's syndrome (ESS).

Methods: A total of 42 pSS patients and 24 healthy donors were enrolled in this study. The ESS model was induced in female wild type (WT), IL-10^{-/-}, recombination activating gene 2 (RAG-2)^{-/-} (CD45.2) and B6.SJL-Ptprca Pepcb/BoyJ (CD45.1) mice. T follicular helper (Tfh) cell migration in vivo was visualized by two-photon confocal microscopy. The identification of acteoside distribution in vivo was analyzed by high-performance liquid chromatography-mass spectrometry system.

Results: We first found negative correlations of IL-10⁺ regulatory Breg cell numbers with disease activity and Tfh cell numbers in pSS patients and ESS mice. In culture, IL-10 suppressed human and murine Tfh cell differentiation by promoting STAT5 phosphorylation. By using an adoptive transfer approach and two-photon live imaging in RAG-2^{-/-} mice, B cell-derived IL-10 critically restrained Tfh cell responses. However, Breg cells from pSS patients and ESS mice showed defective inhibitory function in the suppression of autologous Tfh cell expansion. Upon drug screening, we showed that acteoside, a caffeoyl phenylethanoid glycoside, could promote IL-10 production from human and murine B cells via TLR4/PI3K axis. Importantly, acteoside treatment effectively increased IL-10⁺ B cells in ESS mice and ameliorated disease pathology accompanied by reduced T effector cells.

Conclusions: These findings demonstrate a role for IL-10-producing Breg cells in pSS pathogenesis, which may serve as a promising target in drug screening.

PD046 / #481

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

EXTRA-CRITERIA CLINICAL MANIFESTATIONS OF APS ARE ASSOCIATED WITH CIRCULATING IMMUNE-COMPLEXES OF B2GP1 BOUND TO ANTIPHOSPHOLIPID ANTIBODIES

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Background and Aims: Circulating immune-complexes (CIC) of beta-2-glycoprotein-I (B2GP1) and anti-B2GP1 antibodies (B2-CIC) were associated to non-criteria APS clinical manifestations in patients with thrombotic APS. In this work we performed a multicenter study on both thrombotic and obstetric APS patients, to analyze clinical features with the presence of B2-CIC . Aim: to evaluate the clinical associations of the presence of B2-CIC in patients with APS, both thrombotic and obstetric.

Methods: A cross-sectional and observational multicenter study was conducted on 303 patients recruited from six hospitals who fulfilled APS classification criteria.

Results: B2-CIC prevalence in APS patients was 39.3%. B2-CIC-positive patients with thrombotic APS presented a higher incidence of thrombocytopenia (OR: 2.32, p=0.007), heart valve disease (OR: 9.06, p=0.015) and triple aPL positivity (OR: 1.83, p=0.027), as well as lower

levels of C3, C4 and platelets ($p < 0.001$) compared to B2-CIC-negative patients. B2-CIC of IgM isotype were significantly more prevalent in obstetric APS (44.8% vs 29.6% $p = 0.023$). Purified IgG from immune complexes recognize B2GP1 in open conformation, but not in closed conformation

Conclusions: Patients with thrombotic events and positive for B2-CIC had lower platelet count and complement levels than those who were negative, suggesting a greater degree of platelet activation. B2-CIC can only be formed after B2GP1 changes its conformation to the open form, a situation that only occurs after its activation. The presence of B2-CIC maybe could be a surrogate marker for the action of a second hit, triggering the protein opening and allowing aPL binding.

PD047 / #297

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

**HIGH PREVALENCE OF AGO1 ANTIBODIES IN SJÖGREN'S SYNDROME PATIENTS WITH
MANIFESTATIONS OF SENSORY NEURONOPATHY**

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Background and Aims: Sjögren's syndrome (SjS) is a heterogeneous disorder frequently accompanied by neurological manifestations, in particular peripheral neuropathies (PN). The biological background of this connection, e.g. antibodies typically occurring with neuropathic manifestations, is poorly understood. Antibodies against argonaute proteins (AGO1 or AGO2) have been detected in subgroups of both SjS and NP in independent cohorts, but never addressed in a combined way. Here, we aim to compare the prevalence of AGO1 antibodies in SjS patients with or without neurological manifestations, in particular sensory neuronopathy (SNN).

Methods: Using indirect ELISA optimized for the detection of AGO1 antibodies, we screened 264 SjS patients, of which 118 (44.7%) showed neurological manifestations, including 18 (6.8%) with sensory neuronopathy (SNN). Prevalences of AGO1 antibodies were statistically compared among the groups.

Results: Among the 264 SjS patients, 21 (8%) had AGO1 antibodies. Among the 118 SjS patients with neurological manifestations, 13 (11%) had AGO1 antibodies, which was not significantly more than among the SjS patients without any known neurological manifestations (8/146, 5.5%; $p = 0.0989$, χ^2). In SjS patients with a SNN manifestation, however, the prevalence of AGO1 antibodies was about six times higher (6/18, 33.0%; $p = 0.0001$, χ^2) than in those without neurological manifestations.

Conclusions: We conclude that the connection between SjS and SNN may be described by a higher prevalence of AGO1 antibodies. A clinical analysis of SjS+SNN patients with or without AGO1 antibodies is ongoing in order to understand if the antibody may be useful for patient stratification or for comprehending disease mechanisms.

PD048 / #136

E-POSTER DISCUSSION 05: CTDS 02
18-03-2023 12:10 PM - 1:10 PM

HLA-DRB1 ASSOCIATION IN ACPA POSITIVE AND ACPA NEGATIVE RHEUMATOID ARTHRITIS IN ALBANIA

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Background and Aims: Rheumatoid arthritis is an inflammatory disease caused by a interplay of genetic variants and environmental exposures. The presence or absence of antibodies to citrullinated peptide antigens has proved to be one of the best clinical predictors of the severity of disease course. The genes have been shown to associate differently with ACPA + and ACPA -. The aim of our study is to provide and compare data for both subsets.

Methods: In this study were included 100 patients with established RA diagnosis as following the 1987 ACR Criteria. The control group included 191 healthy blood donors. The DRB1 allele frequencies in the RA subsets were compared with the respective frequencies of the control group. Serum ACPA levels were measured using an ELISA method. HLA-DRB1 genotypes, defined at the first field level, were determined using molecular biology methods.

Results: ACPA positivity was detected in 48% of RA patients and in 3.6% in control group. A statistically significant difference was found for the DRB1*04 between the healthy donors (N=30 compared to ACPA+ (N=18), (p=0.0006) and ACPA+ / RF+ (N=15), (p=0.0004). For ACPA- (N=15) and ACPA-/RF+ (N=11) we have found the significant difference for the DRB1*07 respectively (p=0.0041) and (p=0.0001). Also the allotype of DRB1*11 displayed protective associations with ACPA+ (p=0.0006) and ACPA- (p=0.04) when we compared with healthy donors (N=86).

Conclusions: In our study we found different association of DRB1 alleles for ACPA+ and ACPA-. The data provide further support for distinct genetic aetiologies of RA subsets.

PD049 / #304

E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
18-03-2023 12:10 PM - 1:10 PM

EFFICACY OF BRODALUMAB IN “DIFFICULT-TO-TREAT AREAS

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Background and Aims: Psoriasis of the scalp, genital areas, and palms and soles represent a treatment challenge in clinical practice. The present is a descriptive study investigating the efficacy of brodalumab in these sites.

Methods: 158 psoriatic patients with scalp involvement, 69 with genital involvement, and 54 with palmoplantar involvement being treated with brodalumab were assessed at weeks 16, 28, and 48 using PSSI (Psoriasis Scalp Severity Index), sPGA-G (Genital Physician Global Assessment) and ppPASI (palmoplantar Psoriasis Area Severity Index)

Results: In scalp psoriasis mean PSSI fell from a baseline of 18.6 (standard deviation (sd) 11.4) to 1.9 (sd 4.6) at 16 weeks. The achievement of relative PSSI was observed already at 16 weeks: 86% achieved PSSI75, 80% PSSI90, and 75% PSSI100. At 24 and 48 weeks a further improvement in response was observed. In genital areas, the mean severity of psoriatic lesions at baseline was 2.2 sPGA-G, at 16 weeks it was 0.2 with further decline at 24 and 48 weeks (0.2 and 0.1). The sPGA-g 0/1 was achieved by 83% of patients at 16 weeks and 100% at 24 and 48 weeks. In the palmoplantar population, the mean ppPASI decreased from a mean of 3.5 (sd 1.9) to 0.2 (0.6) at 48 weeks. At 16 weeks ppPASI75, 90, and 100 had all been reached by 76.9% at 24 weeks 84.6% of patients had reached all relative ppPASI, a result maintained at 48 weeks.

Conclusions: Brodalumab proved to be effective and safe in the treatment of scalp, genital and palmoplantar regions.

PD050 / #312

E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
18-03-2023 12:10 PM - 1:10 PM

THE IMPACT OF SINGLE NUCLEOTIDE POLYMORPHISMS IN MTHFR AND MTRR GENES ON THE DISEASE ACTIVITY IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background and Aims: Although methotrexate (MTX), a folic acid antagonist, is the anchor drug for juvenile idiopathic arthritis (JIA), up to 30% of patients fail to respond to the treatment or experience its side effects. The aim of our study was to determine the association between single nucleotide polymorphisms (SNPs) in *MTHFR* (rs1801133) and *MTRR* (rs1801394) genes on the disease activity and presence of MTX therapy adverse events in Polish children with JIA.

Methods: The study group included one hundred JIA patients treated with MTX. Demographic and clinical parameters were collected at the baseline of MTX therapy and on a control visit 4-6 months after treatment initiation. SNPs genotyping was performed using genomic DNA isolated from peripheral blood samples.

Results: In comparison with CC individuals, patients with *MTHFR* rs1801133 CT/TT variant had significantly higher values of inflammatory markers (ESR 34.00 vs 16.00 p=0.02; CRP 8.00 vs 3.20, p=0.02), number of joints with active arthritis (2.00 vs 1.00, p=0.04) and JADAS-71 value (14.50 vs 11.40, p=0.02) at the baseline of MTX treatment. Children with *MTRR* rs1801394 AG/AA variant presented significantly higher inflammatory markers values at the moment of JIA diagnosis than GG individuals (ESR 26.00 vs 8.00 p=0.004; CRP 8.00 vs 0.70, p=0.005). Neither of the SNPs was associated with efficacy and adverse effects of MTX.

Conclusions: *MTHFR* rs1801133 and *MTRR* rs1801394 polymorphisms are associated with higher disease activity at the moment of JIA diagnosis.

PD051 / #397

E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
18-03-2023 12:10 PM - 1:10 PM

**THE OMERACT VALIDATION PROCESS OF ULTRASOUND FOR ASSESSMENT OF CPPD:
WHAT'S NEXT? A SCORING FOR CPPD EXTENT!**

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Background and Aims: No validated grading systems have yet been developed allowing for quantification of the extent of crystal deposition in CPPD. The aims of this study were to develop a consensus-based US scoring system for CPPD according to the OMERACT methodology, and test its reliability.

Methods: A Delphi survey was circulated among the members of the OMERACT US group, including statements on the sites to be included in the scoring, the scanning technique and the scoring for single structures. Agreement was achieved when 4 and 5 grades of a Likert scale reached $\geq 75\%$ of concordance. Subsequently, 2 rounds of a web-based exercise were conducted on 120 static images representing equally all degrees of crystal deposition. In the second step of the validation process, 2 rounds of a patient-base exercise were conducted on 8 patients by 7 experts using the novel scoring system. Intra- and inter-reader reliability was assessed using weighted kappa statistics.

Results: 3 Delphi rounds were needed to reach agreement on all items. Knees and wrists were included in the final score, using a four-grade scoring system (**Figure1**). The inter- and intra-reader reliability ranged from substantial to almost perfect in static images and substantial on patients (**Figure2**).

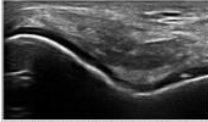
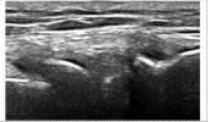
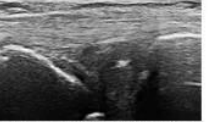
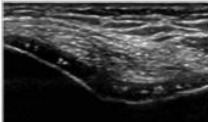
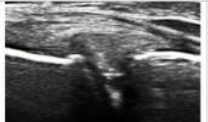
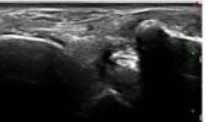
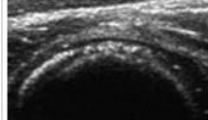
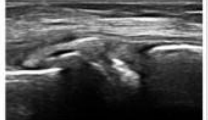
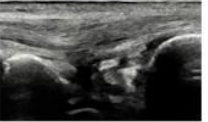
The OMERACT US scoring system for CPPD

The OMERACT definitions for US detection of CPPD (Filippou G et al, Ann Rheum Dis 2018) should be applied for the scoring system.

Technical notes:

- The evaluation of CPP deposits should be performed on a large portion of the structure under examination, according to the US acoustic window, evaluating the entire structure without lifting the probe (for example entire HC of the femur)
- The scoring of CPP deposition should be assessed on the frame with the highest grade of deposits (reference image)
- Each structure should be evaluated using a multiplanar approach (scanning at least in two perpendicular planes)

	Med Meniscus	Lat Meniscus	HC	TFCC	Sum
Right Knee					
Left Knee					
Right Wrist					
Left Wrist					
Total Patient Score					

KNEE HYALINE CARTILAGE	KNEE MENISCUS	WRIST TFCC
GRADE 0: no images consistent with CPPD		
GRADE 1: ≤3 single spots or 1 small deposit		
		
GRADE 2: > 3 single spots or >1 small deposit or ≥1 larger deposit occupying ≤ 50% of the structure under examination in the reference image		
		
GRADE 3: deposits that occupy more than 50% of the structure under examination in the reference image		
		

Reliability on static images		kappa	Agreement
Inter-observer	menisci	0.71	Substantial
	HC	0.86	Almost perfect
	TFCC	0.60	Moderate
	Overall	0.72	Substantial
Intra-observer	menisci	0.82	Almost perfect
	HC	0.89	Almost perfect
	TFCC	0.73	Substantial
	Overall	0.82	Almost perfect
Reliability on patients		kappa	Agreement
Inter-observer	menisci	0.70	Substantial
	HC	0.77	Substantial
	TFCC	0.34	Fair
	Overall	0.66	Substantial
Intra-observer	menisci	0.75	Substantial
	HC	0.87	Almost perfect
	TFCC	0.35	Fair
	Overall	0.72	Substantial

Conclusions: This study represents a fundamental step in the OMERACT process of validating US as an outcome measurement instrument. The scoring demonstrated that it was clear and easily applicable. This study and the above proposed scoring system will hopefully provide a useful tool for clinical practice and research.

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E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
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**MODULATION OF NEUTROPHIL FUNCTION BY RECOMBINANT HUMAN IGG1 FC
HEXAMER IN THE ENDOGENOUS K/BXN MOUSE MODEL OF RHEUMATOID ARTHRITIS**

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Background and Aims: Neutrophils are a pivotal cell type driving rheumatoid arthritis. Neutrophils are known to infiltrate the joints and are readily activated by immune complexes (ICs) via their Fc-gamma receptors (FcγRs) to release IL-1β, which induces cartilage damage. Thus, FcγR-expression on neutrophils is of crucial importance in the perpetuation of the arthritis. Due its high avidity binding to FcγRs, we aimed to investigate the potential anti-inflammatory effect of a recombinant IgG1 Fc-hexamer (rFc-μTP-L309C) on neutrophils in the K/BxN mouse model of endogenously generated chronic arthritis.

Methods: Two hundred mg/kg of rFc-μTP-L309C and human serum albumin (HSA), used as a control, were administered subcutaneously every other day. Mouse ankle joints were monitored daily to generate a clinical score. Immunohistology was used to evaluate neutrophil infiltration and TUNEL to assess apoptosis. ELISA was used to measure IL-1β.

Results: Treatment with rFc-μTP-L309C, but not HSA, was able to significantly ameliorate the arthritis in the K/BxN mice. Neutrophil infiltration into the ankle joint was found but treatment with rFc-μTP-L309C resulted in significantly less neutrophil infiltration. There was no significant influence of rFc-μTP-L309C on neutrophil death/apoptosis. Significantly less IL-1β was measured in the synovial fluid of mice treated with rFc-μTP-L309C.

Conclusions: Amelioration of the arthritis in the K/BxN mouse model can be explained in part by inhibition of neutrophil infiltration into the joints as well as inhibition of IL-1β production. Given the observed inhibitory properties on neutrophils, rFc-μTP-L309C may be a potential therapeutic candidate to treat inflammatory conditions whereby neutrophils are the predominant cell type involved in the pathogenesis.

PD053 / #305

E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
18-03-2023 12:10 PM - 1:10 PM

RISANKIZUMAB SHOW FASTER RESPONSE IN BIO NAÏVE THAN IN BIO-EXPERIENCED PSORIATIC PATIENTS

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Background and Aims: Risankizumab is an approved biological therapy for moderate-to-severe plaque psoriasis; and psoriatic arthritis. It showed safety and efficacy in numerous real-world experience. Previous biological treatment, obesity and joint involvement seems to undermine clinical response.

Methods: We retrospectively analyzed 136 patients from 11 centers in Italy who undergone Risankizumab for psoriasis. The proportion of patients achieving a 100%, 90%, 75% of improvement in Psoriasis Area Severity Index (PASI) and PASI<3 were collected at weeks 16, 28, 40 e 52, absolute DLQI (dermatology life quality index) and DLQI (0/1) at baseline and week 40 and 52 was collected

Results: At the time of analysis 228, 188, 151 and 117 patients had completed 16, 28, 40, and 52 weeks of treatment, respectively. The mean PASI score decreased from 14.8 ± 7.2 at baseline to 2.7 ± 3.8 at week 16. Similar reductions were observed when considering PASI<3, PASI75, PASI90, and PASI100. MeanDLQI fall from 19.4 to 1 and 0.8 at week 40 and 52 respectively. No substantial difference was detected between obese patients and non obese, similar results was observed in psoriatic arthritis population. Bio-naïve patients response significant better at week 16, 28 in the achievement of PASI90, and at week 28 and 40 in the achievement of PASI75 and <3.

Conclusions: Risankizumab seems to be faster in the clinical response in bio-naïve patients, significant difference tend to reduce at 1-year of treatment.

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E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
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COMPARISON OF THE EFFICACY OF TUMOR NECROSIS FACTOR INHIBITORS AND INTERLEUKIN 17 INHIBITOR IN PATIENTS WITH PSORIATIC ARTHRITIS

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Background and Aims: Psoriatic Arthritis (PsA) is a chronic autoimmune disease presenting with a diverse clinical phenotype, so the choice of appropriate treatment is challenging. The aim of this study is to compare treatment response of tumor necrosis factor inhibitors (TNFi) and interleukin 17 inhibitor (IL17i) in PsA over a period of 12 months.

Methods: A single center, observational study of 103 consecutive PsA patients who were treated with TNFi (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol) and IL17i for at least 12 months. Treatment response was evaluated by Disease Activity Index for Psoriatic Arthritis (DAPSA score).

Results: A total of 103 patients were included, 77 received monotherapy with TNFi and 26 IL17i. The mean age (55.54 ± 12.35 vs 59.11 ± 10.86 years, $p=0.19$), disease duration (7.85 ± 7.13 vs 8.49 ± 7.16 years, $p=0.69$), baseline DAPSA score (18.16 ± 11.29 vs 20.58 ± 7.46 , $p=0.4$) were comparable between two groups and 58.2% were women. Baseline patient distribution across remission (0% vs 0%), low disease activity (LDA) (17.16% vs 2.24%, $p=0.054$), moderate disease activity (MDA) (32.84% vs 13.43%, $p=0.06$) and high disease activity (HDA) (7.46% vs 3.73%, $p=0.5$), according to DAPSA score was comparable between treatment groups. The proportion of patients reaching DAPSA remission at 12 months was significantly higher for patients treated with TNFi compared with IL17i (41.04% vs 11.19%, $p=0.005$). Within-group the mean(SD) change in DAPSA score from baseline to twelfth month was statistically significant for both TNFi ($\Delta: 18.16-3.76=14.4$ (1.33), $p<0.001$) and IL17i ($\Delta: 20.58-5.52=15.06$ (1.79), $p<0.001$).

Conclusions: Both treatment arms induced significant improvement in DAPSA score. However, we observed significantly higher proportion of DAPSA remission for the group of TNFi compared to IL17i.

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**AVERAGE TREATMENT EFFECT (ATE) ANALYSIS OF SOLID AND HEMATOLOGIC
CANCER IN SPA PATIENTS TREATED WITH TNF-INHIBITORS AND ANTI-INTERLEUKIN:
DATA FROM THE GISEA REGISTRY**

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Background and Aims: The aim of the current study is to investigate the occurrence of solid and hematologic cancer among Spondyloarthritis patients enrolled in the Italian GISEA Registry and treated with TNF-inhibitors (TNFi), anti-interleukin17 or interleukin12/23 monoclonal antibodies (antiIL), with the aid of machine learning.

Methods: SpA patients from the GISEA Registry were divided into groups according to pharmacological exposure: no treatment (G0), TNFi-treated (G1) and antiIL-treated (G2). In every group, prevalence and incidence of overall, solid, and hematologic cancer were evaluated. Patient profiling for the ATE analysis included all clinical and demographic information shown in table 1; the main outcome was the relative risk (RR) of cancer in relation to bDMARD exposure.

Results: The multi-center Italian GISEA cohort comprised 4458 SpA patients recruited from 2010 to 2022. Prevalence and incidence of overall and solid malignancies was significantly different among groups, being highest in Group 0. The ATE analysis found a significantly higher RR of solid and overall malignancies in the no treatment group compared to TNFi (solid cancer: RR G1vsG0=0,42, CI 0,20-0,85) and antiIL (solid cancer RR G2vsG0=0,26, CI 0,08-0,71). Interestingly, TNFi treatment bared a higher RR of overall and solid cancer than antiIL (solid cancer RR G2vsG1=0,61 CI 0,33-0,96). No significant treatment-related risk of hematologic malignancy was detected.

Conclusions: The latest data from the Italian GISEA registry confirms the safety of TNFi and antiIL treatment regarding the occurrence of solid and hematologic cancer. A slightly higher treatment-related risk of solid cancer was found for antiTNFi.

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ASSOCIATION OF SERUM LEVELS OF AICAR AND THE RS2372536 POLYMORPHISM IN THE ATIC GENE WITH THERAPEUTIC RESPONSE TO METROTEXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background and Aims: In Rheumatoid Arthritis (RA) patients, therapeutic failure to metrotexate (MTX) of 52% has been reported. Increase of the 5-aminoimidazol-4-carboxiamide ribonucleotide transformylase (AICAR) leads to a high production of adenosine with the suppression of diverse inflammatory responses. rs237253 polymorphism of *ATIC* gene might be implicated in therapeutic response to MTX in patients with RA. To evaluate the association of the serum levels of AICAR and the rs2372536 polymorphism in the *ATIC* gene with therapeutic response to MTX in patients with RA.

Methods: Cases and controls. 71 patients with diagnosis of AR treated with MTX for at least three months were included. Disease activity was measured by DAS28-VSG. The patients were divided into two groups: a) responders to MTX (DAS28-VSG <3.2) and b) nonresponders (DAS28-VSG ≥ 3.2). Serum levels of AICAR were quantified by ELISA and genotyping was performed with qPCR. The risk the genotypes provide for response was determined with Odds Ratio (IC 95%) and a statistic significance of ≤ 0.05.

Results: From the 71 patients with AR, the nonresponders group presented higher serum levels of AICAR compared to responders (195.35 pg/mL vs 116.8 pg/mL, p=0.046). Frequencies of genotypes in nonresponders vs responders were GG: 18% vs 29%, GC: 41% vs 41%; CC: 41% vs 30% (p=0.949). It was determined that the polymorphic genotype does not provide risk for therapeutic response (OR=1.20, IC95%=0.32-4.42, p=0.78).

Conclusions: Serum levels of AICAR are associated to the therapeutic nonresponse to MTX in AR. Association between therapeutic response and rs2372536 polymorphism of *ATIC* gene was not found.

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PARAMETERS ASSOCIATED WITH INCREASED CAROTID INTIMA MEDIA THICKNESS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND LOW CARDIOVASCULAR RISK

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Background and Aims: The prevalence of increased carotid intima-media thickness (IMT) is increased in patients with rheumatoid arthritis (RA) even at low cardiovascular risk (CVR). This is caused by various reasons: subclinical atherosclerosis, metabolic disorders, and inflammation. **Aims:** To identify the parameters associated with increased carotid IMT in RA patients with low CVR.

Methods: One hundred and thirty three RA patients (female/male 125/8) with low CVR were included in the study. The median age was 49[46;52] years, DAS28 was 4,5 [3,5; 5,0] points. CVR was calculated using the mSCORE, ASSING, QRISK3, ERS-RA scales.

Results: An increased carotid IMT was found in 47% of RA patients with low CVR. The groups of RA patients with low CVR with and without increased carotid IMT did not differ in gender, duration and activity of RA. Patients with increased IMT were older (51[48;53] years) and more likely to have dyslipidemia (60%) compared with patients without increased IMT (29%, respectively, $p < 0,05$ in both cases). Positive correlations of carotid IMT were established with age ($R=0,38$), CVR value determined by mSCORE ($R=0,44$), ASSING ($R=0,41$), QRISK3 ($R=0,41$), ERS-RA ($R=0,45$), the total cholesterol levels ($R=0,21$), the LDL-cholesterol levels ($R=0,23$), the leptin levels ($R=0,21$), systolic blood pressure ($R=0,18$) and diastolic blood pressure ($R=0,22$), $p < 0,05$.

Conclusions: An increase in carotid IMT was seen in about one half of RA patients with low CVR. Parameters associated with an increase carotid IMT in RA patients with low CVR included age, dyslipidemia, levels of total cholesterol, LDL-cholesterol, leptin, systolic blood and diastolic blood pressures.

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E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
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**GENDER AND IMAGING PROGRESSION IN EARLY AXIAL SPONDYLOARTHRITIS:
RESULTS FROM A 48-MONTH FOLLOW-UP (ITALIAN ARM OF SPACE STUDY)**

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Background and Aims: Gender differences in disease presentation and imaging features of axial-spondyloarthritis (axSpA) have not been thoroughly investigated. We aimed to assess the influence of gender on spinal/pelvic radiographic progression and magnetic-resonance-imaging (MRI) features in early-stage axSpA.

Methods: Baseline data-analysis of the Italian SPACE-cohort, including patients with chronic-back-pain (CBP; duration ≥ 3 months and ≤ 2 years; onset < 45 years). Patients underwent MRI and X-rays of the sacroiliac joints (SIJ) to establish diagnosis of axSpA (ASAS-criteria). Clinical features, disease-activity and functional indices, imaging were collected at baseline and yearly during 48-months. Spinal and SIJ X-rays and MRIs were scored by 2 readers following: SPARCC, mSASSS and mNY-criteria. Characteristics of axSpA patients according to gender were compared over-time using descriptive-statistics or Mann-Whitney U-Test/t-test for continuous-variables and chi-square/Fisher's exact test for dichotomous-variables.

Results: Ninety-one patients had axSpA (83.5% non-radiographic; 16.5% radiographic); 47.3% male. Males were younger with less axial symptoms duration, had more frequently HLA-B27+, radiographic sacroiliitis with bilateral/symmetric pattern and signs of spondylitis. Females were more frequently associated with peripheral/enthesal involvement and non-radiographic form. Overall, we observed a decrease —albeit slightly less so in females— in functional and disease-activity indices. Males showed greater pelvic/spinal radiographic progression and had more frequently active sacroiliitis on MRI than females (**Fig. 1A-E**). Although the frequency of inflammatory-corner-lesions did not differ between males and females, the localization varied: more cervical/thoracic MRI-spine lesions in females, more lumbar lesions in males. We observed a significant downtrend of SPARCC-SIJ/spine scores in all patients, irrespective of gender. More *fat-lesions* were observed on MRI-spine in females, more *fat-lesions* on MRI-SIJ in

males(Fig.1F-

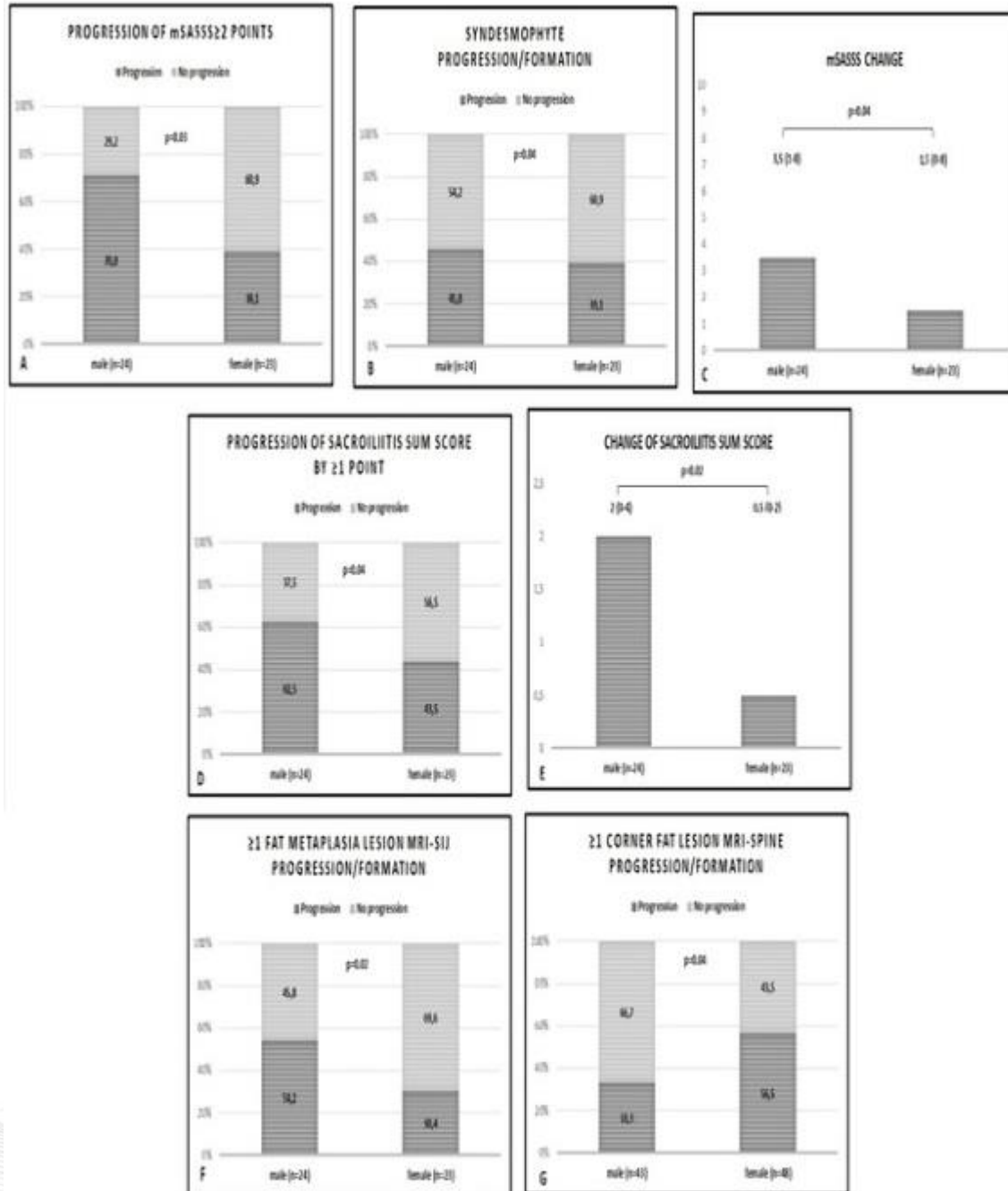


Figure 1 A-G: Association of gender with spinal and SII radiographic progression and fat lesions on MRI in axSpA after 48-months of follow-up.

G).

Conclusions: Gender was associated with distinct axSpA features; females showed low-grade radiographic sacroiliitis and spinal progression and a higher prevalence of cervical/thoracic spine-MRI signs.

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E-POSTER DISCUSSION 06: INFLAMMATORY ARTHRITIS
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EMERGENCE OF BIOSIMILARS IN THE US

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Background and Aims: Biosimilars are due to make a more widespread appearance on the US market over the next two years, particularly as the world’s top grossing drug, AbbVie’s adalimumab, goes off patent in 2023. This study aims to assess US rheumatologists’ current attitudes and opinions of the biosimilar landscape.

Methods: An independent market analytics firm surveyed 80 US rheumatologists via an online survey platform from May 5 through May 13, 2022.

Results: Rheumatologists are unenthusiastic about biosimilars. Only one-third express favorable perceptions of these products, but indicate comfort around the safety, efficacy, and immunogenicity evidence required to achieve biosimilar designation. Rheumatologists indicate higher comfortability initiating a biosimilar when presented with biologic naïve patients or circumstances in which a switch is medically required as opposed to switching for non-medical reasons.

	Extremely comfortable
Efficacy	60%
Safety	53%
Immunogenicity	35%

	Extremely comfortable
Initiating a biologic naïve patient on a biosimilar	71%
Initiating a biologic switch patient on a biosimilar when the switch is medically required	56%
Initiating a non-medical switch from a branded therapeutic to a biosimilar	33%

Despite current hesitations to adopt, rheumatologists are aware of the adalimumab biosimilars and express a likelihood of prescribing over branded adalimumab. Physicians anticipate allocating two-fifths of adalimumab prescriptions to biosimilars once all the FDA approved biosimilars are available in 2023. High concentration formulations and autoinjectors are reported to be influential features in driving prescribing.

Anticipated Prescription Volume <i>Mean % of prescriptions</i>	
Adalimumab Brand	Adalimumab Biosimilars
60%	40%

Conclusions: Rheumatologists' skepticism is counter balanced with favorable anticipated uptake of adalimumab biosimilars.

PD060 / #111

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VALIDATION OF THE CUSP THEORY IN HLA-DISEASE ASSOCIATION: A TALE OF THREE ALLELES

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Background and Aims: Distinct alleles of human leukocyte antigen (HLA) have been found to be major genetic risk factors in many human diseases, but the mechanisms underlying the associations are unknown. Over the past decade, my group has proposed and studied a novel concept, named the *Cusp Theory*. The theory proposes that the HLA cusp region is enriched in allele-specific signal transduction ligands that interact with non-MHC cell surface receptors and trigger signaling events independent of antigen presentation (AP).

Methods: No methods (Review)

Results: Our empirical evidence that validates the Cusp theory: *DRB1*04:01*, is a major risk factor for rheumatoid arthritis. Our findings indicate that the cusp region - called also the “shared epitope” (SE) - coded by this allele acts as a signal transduction ligand that interacts with a defined binding site on cell surface calreticulin (CRT), and activates pro-arthritic signaling and transcriptomes. Synthetic inhibitors of SE-CRT interaction have potent therapeutic effects in experimental arthritis models and are presently studied in human trials. Alleles known to protect against RA that express a *70-DEAAA-74* sequence exert anti-inflammatory and pro-M2 polarization effects in an AP-independent manner. Allele *DRB1*03:01* - the single most significant risk factor for systemic lupus erythematosus – activates AP-independent characteristic lupus transcriptome and cellular aberrations, including endoplasmic reticulum stress, unfolded protein response, mitochondrial dysfunction, and necroptotic cell death. In *DRB1*03:01* transgenic mice, that sequence triggers anti-DNA antibodies, immune complex deposition and lupus nephritis.

Conclusions: These findings lend support to the Cusp theory and may help to identify new therapeutic strategies for HLA-associated diseases.