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Reproductive issues in rheumatology

OP0326

DEVELOPMENT OF A STANDARDIZED MINIMAL CORE DATA SET FOR PREGNANCY REGISTERS IN RHEUMATOLOGY – RESULTS OF A EULAR TASK FORCE

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Background: Results from individual data collections on drug safety during pregnancy and outcomes of pregnancy in patients with inflammatory rheumatic diseases (IRD) are often limited due to small number of cases. Joint data analyses from different data sources could solve this problem.

Objectives: The aim of this EULAR task force was to define a core data set to facilitate joint analysis of pregnancy registers in rheumatology.

Methods: Scope and core areas of the core data set have been developed according to COS-STAD recommendations¹ by consensus. An initial list of data items possibly relevant for pregnancy registers was generated based on (I) a systematic literature search, (II) data items already collected by European pregnancy registers and (III) a survey amongst patient representatives. Consensus about the importance of each data item to be included in a core data set was reached by applying a 2-round Delphi survey where each item was rated on a numeric scale (1-3 = low importance, 4-6 = important but not critical, 7-9 = critical importance). Any data item that was considered as 'critical important' by at least 70% of responders in Delphi round 2 was included in the core set. During a face-to-face meeting of the EULAR task force, the inclusion or exclusion of data items with no consensus was finally decided.

Results: The scope was defined as follows: 'To develop a standardized core data set for data collection in prospective observational research and clinical care of pregnant women with IRD including the neonatal phase. All interventions the women receive will be covered. Patients should be enrolled at the earliest possible moment during pregnancy, and data should ideally be collected once every trimester. An additional visit should capture the neonatal phase'. Three core areas were described: 'Maternal information' (including demographics, IRD disease characteristics and comorbidities), 'Pregnancy' (including prior and current pregnancy(ies), delivery and neonatal outcomes) and 'Treatment' (including medication of IRD and other health conditions).

64 experts from 14 different European countries participated in the 2 rounds of Delphi (68% female; 84% physicians, 5% obstetricians, 5% epidemiologists, 3% patients, 3% midwives). Of the 148 data items, 85 were included in the final core set. The figure shows included items within the core areas.

Suggestion of items for a core data set for pregnancy registers in rheumatology		
MATERNAL INFORMATION	PREGNANCY	TREATMENT
Demographics Maternal age at conception Maternal body weight and height Maternal educational level and professional training Smoking and alcohol consumption during pregnancy	Prior pregnancy(ies) Number of prior pregnancy(ies) and parity Prior pre-eclampsia, eclampsia or HELLP syndrome Number of prior pregnancy losses (including spontaneous abortion, fetal death and stillbirths) Prior (preterm) delivery Congenital malformations of prior born infant(s)	Treatment 12 months prior to conception DMARD use Oral glucocorticoid use Use of potentially teratogenic medication
IRD disease characteristics Diagnosis Fulfillment of classification criteria Disease duration Prior important IRD medication(s) Physician reported disease severity Disease activity estimated with appropriate index ^a Physician reported disease activity Flares during pregnancy Patient reported disease activity Patient reported global health Disease-specific auto-antibodies and activity markers ^b	Current pregnancy Planned pregnancy Use of assisted reproduction Estimated date of conception Indication of singleton or multiple pregnancy Comorbidities: arterial hypertension, gestational diabetes and thrombotic events Pre-eclampsia, eclampsia or HELLP syndrome Intrauterine growth restriction	Treatment of IRD during pregnancy DMARD use with name, dose and application interval, start and stop dates and reasons for stopping Oral glucocorticoid use with dose and application interval, start and stop dates Intravenous glucocorticoid use with application date NSAID use with application date
Concomitant diseases and adverse events Selected comorbidities: rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, Diabetes mellitus, hypertension, Heart disease, thrombotic events Maternal serious adverse events ^c Maternal death with date and cause of death	Delivery/Outcome Live birth Elective termination with reasons and WGA Perinatal loss with WGA Gestational age at birth Mode of delivery Placental/premature rupture of membranes Neonatal outcome Birth weight Gender Breastfeeding Congenital malformations, congenital heart block Chromosome abnormalities Hospital admission Neonatal death	Treatment of other health conditions during pregnancy Use of folic acid, antithrombotic drugs, aspirin, heparin or other anticoagulants

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; HELLP, hemolysis, elevated liver enzymes and low platelets; NSAID, non-steroidal anti-inflammatory drug; pre-, previous; WGA, whole genome amplification.

^a The EULAR task force will find additional consensus on disease specific auto-antibodies and markers including activity, level of severity or inflammation of the disease in a companion comparison of 50 patients.

Conclusion: The consensus process resulted in an extensive list of data items recommended by experts to be collected as a minimum by pregnancy registers in rheumatology. This core data set applies to all pregnant women irrespective of the

underlying IRD. The EULAR task force plans to find consensus on additional disease specific advice.

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The future of therapeutic strategies

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FECAL MICROBIOTA TRANSPLANTATION IN SYSTEMIC SCLEROSIS: A DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED PILOT TRIAL

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Background: Systemic sclerosis (SSc) is a progressive, multi organ, autoimmune disease marked by frequent and severe gastrointestinal (GI) afflictions and gut dysbiosis.

Objectives: Determine the safety and efficacy of fecal microbiota transplantation (FMT) using commercially-available anaerobic cultivated human intestinal microbiota (ACHIM) in patients with SSc.

Methods: The trial was a single-center, randomized, double-blind, placebo-controlled 16-week pilot of FMT by gastroduodenoscopy of ACHIM in SSc conducted at Oslo University Hospital. Primary endpoints were safety and clinical efficacy on GI symptoms assessed at weeks 4 and 16. Safety was assessed by observation, interviews and standardized safety form. Efficacy on GI symptoms was measured using the UCLA GIT 2.0 score questionnaire. Patients were defined as responders if reported symptom improvement was equivalent to the UCLA GIT definition of "minimally clinically important difference". Secondary and explorative endpoints included changes in relative abundance of total, immunoglobulin (Ig)A- and IgM-coated fecal bacteria measured by 16s rRNA sequencing; changes in modified Rodnan skin score, lung function, CRP, ESR, and patient and physician global. Descriptive statistics were applied for clinical endpoints and linear mixed models for microbial analysis.

Results: Ten patients with limited cutaneous SSc randomized to ACHIM (n=5) or placebo (n=5) were included. All patients were female with clinical apparent GI symptoms, mean age of 62 years and mean time from diagnosis of 12 yrs. Two placebo controls experienced procedure-related serious adverse events; one developed laryngospasms at first gastroduodenoscopy necessitating study exclusion, one duodenal perforation at final gastroduodenoscopy. Improvement in total GIT score was reported by 3/5 FMT patients compared to 2/4 placebo controls at weeks 4 and 16 (Figure 1). FMT effects were most pronounced on lower GI symptoms, with improvement reported by 5/5 FMT patients with diarrhea, distention/bloating and/or fecal incontinence at baseline compared to 2/4 placebo controls (Figure). Clinical secondary endpoints showed no differences and other side effects (stomach discomfort, bloating and diarrhea) were mild and transient. Fecal microbiota diversity (observed number of operational taxonomic units) was increased after FMT compared to placebo treatment at week 16 (p<0.006). Moreover, abundant bacterial genera in ACHIM were present within the total, and IgA- and IgM-coated fecal bacteria at both week 4 and 16 in the FMT group (Figure 2) but not in the placebo controls.

Clinical effect of FMT in SSC measured by the UCLA GIT score

Stackplot of significantly changed relative abundance of fecal bacteria after FMT from week 0 to weeks 4 and 16

Conclusion: FMT of commercially-available ACHIM in patients with SSC appeared safe, effectively reduced lower GI symptoms, altered gut microbiota composition, richness and diversity and appeared to affect the mucosal immune system

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Calming the cytokine storm in children and adults__

OP0328

COMPARISON OF SERUM CYTOKINE PROFILE IN MACROPHAGE ACTIVATION SYNDROME AMONG DIFFERENT BACKGROUND RHEUMATIC DISEASES IN CHILDREN:

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Background: Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of pediatric rheumatic diseases. MAS occurs most often in children with systemic juvenile idiopathic arthritis (s-JIA) and less commonly in children with systemic lupus erythematosus (SLE), Kawasaki disease (KD) and juvenile dermatomyositis (JDM). The hallmark of MAS includes uncontrolled and dysfunctional immune responses involving continual activation and expansion of T lymphocytes and macrophages, which in turn lead to marked hypercytokinemia. However, it is still unknown which cytokines play a key role in the pathogenesis of MAS among different backgrounds.

Objectives: This study was aimed to clarify cytokines involved in the development of MAS among different background rheumatic diseases and to identify the serum biomarkers for the diagnosis of MAS.

Methods: Serum neopterin, interleukin (IL)-18, IL-6, tumor necrosis factor (TNF)- α and soluble TNF receptor type I (sTNFR-I) and sTNFR-II levels were determined using enzyme-linked immunosorbent assay in 112 s-JIA patients including 30 with MAS, 8 SLE patients including 3 with MAS, 67 KD patients including 4 with MAS, and 7 JDM patients including 3 with MAS. Cytokine profiles in MAS phase of each disease were compared to those in active phase.

Results: Serum neopterin levels in patients with s-JIA, SLE and KD were significantly elevated in MAS phase compared to those in active phase. Serum neopterin levels in patients with JDM were also elevated in MAS phase compared to those in active phase, although statistically significant. Serum sTNFR-I levels in patients with s-JIA and SLE were significantly elevated in MAS phase compared to those in active phase. Serum sTNFR-I levels in patients with KD and JDM were

also elevated in MAS phase compared to those in active phase, although statistically significant. Serum sTNFR-II levels in patients with s-JIA and KD were significantly elevated in MAS phase compared to those in active phase. Serum sTNFR-II levels in patients with JDM were also elevated in MAS phase compared to those in active phase, although statistically significant. Serum IL-18 levels in patients with s-JIA were significantly elevated in both active and MAS phase compared to those in patients with other diseases. There were no significant differences of serum IL-6 and TNF- α levels among different backgrounds.

Conclusion: The elevation of serum neopterin levels was the common finding in patients with MAS even in different backgrounds. These findings indicate that overproduction of interferon (IFN)- γ might be closely related to the development of MAS. Serum neopterin levels which reflect IFN- γ production might be a promising biomarker for the disease activity of MAS.

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OP0329

PLCGAMMA2/TMEM178 DEPENDENT PATHWAY IN MYELOID CELLS MODULATES THE PATHOGENESIS OF CYTOKINE STORM SYNDROME

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Background: Cytokine storm syndrome (CSS) is a life-threatening condition, observed in several rheumatic diseases, and a well-known complication of systemic juvenile idiopathic arthritis (sJIA) (1). Defects in T cell cytotoxicity leading to their excessive activation are major contributors to CSS development. However, dysregulated innate immune responses are also observed (2). The role of monocytes and macrophages as drivers of CSS, regardless of T cells, and the signaling pathways regulating monocyte/macrophage responses, have not been formally investigated.

Objectives: The goal of this study was to determine the contribution of monocytes/macrophages to the development of CSS and analyze the signaling pathways that lead to aberrant monocyte/macrophage pro-inflammatory responses using animal models of the disease and patient samples.

Methods: To study the involvement of monocytes/macrophages in a T cell-dependent model of CSS we treated LCMV-infected Perforin-/- mice with clodronate-liposomes or neutralizing anti-CSF1Ab prior to disease initiation. Similar depletion experiments were performed in a T-cell independent CSS model consisting of five injections of the TLR9 agonist CpG-1826 into WT mice. Myeloid cell contribution to CSS was assessed in mice with LysMCre-driven deletion of Plcy2 or global deletion of Tmem178, a downstream Plcy2 target gene specifically expressed in macrophages. Presence of immune infiltrates in liver and spleen was evaluated by FACS analysis and immunohistochemistry, circulating inflammatory cytokine levels were detected by ELISA, multi-organ damage was evaluated by histology.

Results: Depletion of monocytes/macrophages during early stages of CSS reduces mortality and inflammatory cytokine levels in both T-cell dependent and independent CSS models. Activation of Plcy2 in myeloid cells controls CSS development by driving macrophage pro-inflammatory responses. Intriguingly, the Plcy2 downstream effector Tmem178 acts in a negative feedback loop to restrain inflammatory cytokine production and protect from CSS development. Highlighting the clinical relevance, Tmem178 levels are reduced in macrophages from mice with CSS or exposed to sJIA patient plasma with active disease.

Conclusion: Macrophages are key drivers of CSS initiation. We identified a novel Plcy2/Tmem178 axis as a modulator of inflammatory cytokine production by monocytes/macrophages in CSS. Reduced Tmem178 levels are observed in sJIA and might be responsible for the increased macrophage pro-inflammatory responses.

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