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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Remission – the holy grail? Looking across diseases

OP0330

COMPARISON OF THE EFFECTS OF DORIS REMISSION AND LUPUS LOW DISEASE ACTIVITY STATE (LLDAS) ON DISEASE OUTCOMES IN A MULTINATIONAL PROSPECTIVE STUDY

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Background: The Definitions of Remission in SLE (DORIS) group has proposed multiple definitions of remission, but these are infrequently attained and have not been prospectively evaluated in relation to protection from damage accrual. In contrast, the Lupus Low Disease Activity State (LLDAS) is more attainable, and has been shown to be associated with improved patient outcomes.

Objectives: To compare the attainability, and association with outcomes, of LLDAS and remission in a prospective multicentre study.

Methods: A prospective multinational cohort study was undertaken in 13 centres between 2013-2017. Time dependent Cox proportional hazards models were used to compare LLDAS and DORIS definitions of remission in terms of impact on disease flares and damage accrual.

Results: 1735 SLE patients were recruited, and followed for (mean±SD) 2.2±0.9 years, totalling 12,717 visits. LLDAS was achieved in 47.2% of observed visits. In contrast, remission was achieved in 1.1%-15.4% of visits depending on the stringency of remission definition. LLDAS attainment at any visit was associated with significantly reduced subsequent flare (HR 0.65, 95%CI 0.56-0.75, p<0.001) and damage accrual (HR 0.59, 95%CI 0.45-0.76, p<0.001). In contrast, only the least stringent remission definition was associated with reduced damage accrual (HR 0.58, 95%CI 0.39-0.88, p 0.01). Only remission definitions including serological remission were significantly associated with reduction in subsequent flares. Patients who spent ≥50% of their observed time in LLDAS had reduction in damage accrual (HR 0.54, 95% CI 0.42-0.70, p<0.001) compared to patients with <50% of observed time in LLDAS; again, only the least stringent remission definition, or the related definition excluding serology, were associated with reduced damage (HR 0.59, 95% CI 0.42-0.83, p 0.003; HR 0.69, 95% CI 0.48-0.99, p 0.05, respectively).

Conclusion: LLDAS was more attainable than any remission definition, whilst still conferring significant reduction in flares and damage accrual. Only the least stringent remission definitions could be shown to be associated with significantly lower damage accrual, likely reflecting a low frequency of remission attainment overall. LLDAS is a valid treatment target for SLE and is more achievable than remission.

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OP0331

MAGNETIC RESONANCE IMAGING TENOSYNOVITIS AND OSTEITIS ARE INDEPENDENT PREDICTORS OF RADIOGRAPHIC AND MRI DAMAGE PROGRESSION IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION

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Background: Progression of structural joint damage occurs in 20-30 % of patients with rheumatoid arthritis (RA) in clinical remission¹. Magnetic resonance imaging (MRI)-detected synovitis and in particular osteitis/bone marrow edema (BME) are known predictors of structural progression in both active RA and in remission, but the predictive value of adding MRI tenosynovitis assessment as potential predictor in patients in clinical remission has not been investigated.

Objectives: To investigate the predictive value of baseline MRI inflammatory and damage parameters on 2 year MRI and X-ray damage progression in an RA cohort in clinical remission, following MRI and conventional treat-to-target (T2T) strategies.

Methods: 200 RA patients in clinical remission (DAS28-CRP<3.2 and no swollen joints) on conventional DMARDs, included in the randomized IMAGINE-RA trial² (conventional DAS28 + MRI-guided T2T strategy targeting absence of BME vs conventional DAS28 guided T2T strategy) had baseline and 2 years contrast-enhanced MRIs of the dominant wrist and 2nd-5th MCP joints and X-rays of hands and feet performed, which were evaluated with known chronology by two experienced readers according to the OMERACT RAMRIS scoring system and Sharp/van der Heijde method, respectively.

The following potentially predictive baseline variables: MRI BME, synovitis, tenosynovitis, MRI and X-ray erosion and joint space narrowing (JSN) score, CRP, DAS28, smoking status, gender, age and patient group were tested in univariate logistic regression analyses with 2-year progression in MRI combined damage score, Total Sharp Score (TSS), and MRI and X-ray JSN and erosion scores as dependent variables. Variables with p<0.1, age, gender and patient group were included in multivariable logistic regression analyses with backward selection.

Results: Based on univariate analyses MRI BME, synovitis, tenosynovitis, x-ray erosion and JSN, gender and age were included in subsequent multivariable analyses. Independent MRI predictors of structural progression were BME (MRI progression) and tenosynovitis (MRI and X-ray progression), see table.

		Dependent variables, progression ≥1 from baseline to month 24 ^a				
		MRI			X-ray	
		MRI Erosion	MRI JSN	MRI combined damage score	X-ray Erosion	X-ray JSN
Explanatory variables	MRI BME	1.13 (1.06-1.21) p<0.001	1.18 (1.08-1.29) p<0.001	1.22 (1.12-1.33) p<0.001		
	MRI Tenosynovitis	1.13 (1.03-1.25) p=0.01	1.21 (1.04-1.40) p=0.01	1.13 (1.02-1.26) p=0.02		1.10 (1.00-1.21) p=0.04
	Age				0.96 (0.93-0.99) p=0.007	

^a: Odds Ratio (95% confidence interval; CI) p-value;

MRI combined damage score: sum score of MRI erosion and JSN scores.