treatment effect, either with 150 mg or 300 mg q4w CAN, was observed by an improvement in the CHQ-PF50 PhS and PsS (increased >5), SF-12 PCS (increased >5) and SDS scores (decreased below 2). At Wk41, the number of patients on CAN was limited (crFMF n=9, HIDS/MKD n=6 and TRAPS n=4) due to the design of the trial (randomised withdrawal part). For the patients who remained on CAN, the improvement in HRQoL, work/school and social life was sustained.

Conclusion: Treatment with CAN led to sustained improvement of HRQoL, work/school and social life in patients with crFMF, HIDS/MKD and TRAPS.

REFERENCES:

- [1] Sahin, et al. *Eur Rev Med Pharmacol Sci.* 2013;17:958–963.
- [2] De Benedetti, et al. *NEJM* 2018;378:1908–1990.

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OP0255

MICROBIOTA TRANSPLANT TO CONTROL INFLAMMATION IN A NLR4-RELATED DISEASE PATIENT WITH RECURRENT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Background: The NLR4 inflammasome activation is essential in host defence, particularly against enteric pathogens. Gain-of-function mutations in *NLR4* are associated with a distinct autoinflammatory syndrome characterized by enterocolitis and recurrent HLH.

Objectives: To report safety and efficacy of faecal microbiota transplantation (FMT) in a patient carrying a *de novo* missense mutations in *NLR4*, with gut inflammation and gut colonization by multi-drug resistant (MDR) pathogens.

Methods: Subject and donors were screened for potential FMT according to Cammarota *et al.* (1) with modifications introduced by Ospedale Pediatrico Bambino Gesù Committee for paediatric FMT procedures. Culture-based and NGS-based microbiota profiling were performed to address MDR persistence and microbial associated communities coupled to inflammatory profiling. After wide donor screening, a universal adult donor was selected and infusion performed twice by colonoscopy from fresh and frozen faeces, respectively. A one year FMT follow up was ensured to address clinical outcomes.

Results: A Caucasian 16 months old boy presented, from 1 month of life, with recurrent HLH, diarrhoea and vasculitic skin lesions, secondary to a *de novo* missense mutation in *NLR4* (I343N). His disease was not controlled despite treatment with repeated high dose of intravenous methylprednisolone pulses and chronic daily glucocorticoid therapy, cyclosporine-A (5 mg/kg) and anakinra (ranging from 5 to 25 mg/kg/day). Because of recurrent HLH episodes, the patient was treated with emapalumab (anti-IFN γ antibody) for three months, with HLH control. However, the patient presented persistent diarrhoea with gut inflammation and colonization by MDR pathogens (*Enterobacter cloacae* and *Enterococcus faecalis*), leading by translocation to systemic infections and, hence, HLH reactivation. Moreover, he developed severe intestinal meteorism with subsequent paralytic-ileus that required ileostomy. Based on the hypothesis that his intestinal dysbiosis concurred in the persistent gut inflammation related to his underlying disease, he received a first FMT with initial clinical improvement. Therefore, ileal anastomosis was performed with recanalization, and a second FMT was performed a month later. The patient did not develop any complication. The stool cultures no longer showed the presence of enteropathogenic germs and since the last FMT (12 months of follow-up) he did not present any symptom of gut inflammation or HLH reactivations.

Conclusion: *NLR4*-related disease is typically characterized by enterocolitis and *NLR4*, highly expressed in intestinal macrophages, is critical for pathogen restriction by phagocytes in the gut lamina propria. The chronic gut inflammation of *NLR4*-patients is a stimulus for systemic inflammation. Moreover, pathogens

present in the gut can trigger HLH episodes. A presence of a selected microbiota from appropriate donor can decrease gut inflammation. FMT may represent a valid and safe therapeutic option in *NLR4*-patients in order to reduce chronic inflammatory stimuli.

REFERENCE:

- [1] Cammarota G. et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut.* 2017 Apr;66(4):569-580.

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OP0256

IN MEDIUM TO LONG-TERM JUVENILE DERMATOMYOSITIS, PROINFLAMMATORY AND PROFIBROTIC CYTOKINES ARE DIFFERENTLY ASSOCIATED WITH PULMONARY INVOLVEMENT IN ACTIVE VS INACTIVE DISEASE

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Background: Knowledge about associations between cytokines and lung involvement in juvenile dermatomyositis (JDM) is scarce.

Objectives: To examine associations between cytokines and pulmonary involvement in JDM assessed after medium to long-term follow-up.

Methods: 58 JDM patients examined median 17y after disease onset were stratified in active and inactive disease by the updated PRINTO criteria (Ref 1). Serum levels of cytokines were analyzed by Luminex or ELISA. Pulmonary function tests (PFT) included forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) (hgb adjusted). PFT variables are expressed as% of predicted. High resolution computed tomography (HRCT) scans were scored for interstitial lung disease (ILD), calcinosis in chest wall and airway disease. Associations between lung involvement and cytokines are presented as Spearman's correlation coefficient (r_s).

Results: Table 1. Characteristics, PFT, HRCT findings and cytokines

	Total (n=58)	Active (n=37)	Inactive (n=21)
Age, y, median (IQ range)	21 (15-34.8)	20 (14-34)	26 (17-37)
Female, n (%)	35 (60)	25 (68)	10 (48)
Disease duration, y (IQ range)	17 (7-27)	16 (6-26)	17 (8-28)
TLC ^a	93 (11)	91 (10)	94 (11)
FVC ^a	96 (12)	94 (12)	99 (12)
DLCO ^a	82 (15)	79 (13)	87 (16)
Any HRCT findings, n (%)	21 (36)	15 (40)	6 (29)
HRCT ILD, n (%)	8 (14)	6 (16)	2 (10)
HRCT calcinosis, n (%)	8 (14)	6 (16)	2 (10)
HRCT airways disease, n (%)	9 (15)	7 (18)	2 (10)
TGF β 1 ^b	29252 (8868)	29698 (9623)	28467 (7513)
PDGF ^b	9083 (2799)	8990 (2979)	9248 (2511)
IP-10 ^b	1448 (1281)	1491 (1438)	1371 (972)
MCP-1 ^b	34 (21)	34 (19)	34 (26)
Eotaxin ^b	138 (103)	142 (108)	132 (95)
IL-17 ^b	15 (14)	15 (15)	15 (10)
IL-5 ^b	1.4 (1.3)	1.6 (1.6)	1.2 (0.5)
MIP1a ^b	2.5 (1.4)	2.7 (1.5)	2.3 (1.1)

Numbers are mean (SD) if not stated otherwise; ^aPFT variables are% of predicted; ^b unit: pg/ml

No significant differences were found between active and inactive patients in tbl. 1.

Associations between cytokines and PFT/HRCT findings

Numbers are r_s , all p 's < 0.05

In patients total, TGF β 1 and PDGF correlated with TLC and FVC (- 0.38 - -0.30). For TGF β 1 correlations with TLC and FVC were - 0.62 and -0.59 in the inactive group, whereas PDGF correlated with FVC in the active group (- 0.48). IP-10 correlated with TLC in active patients only (- 0.35).

In patients total and active patients, eotaxin correlated with DLCO% (0.39 and 0.52). In inactive patients, MIP1b correlated with DLCO% (0.47). In patients total, IP-10 correlated with any HRCT finding and airways disease (0.37 and 0.44); which were also present in active patients (0.34 and 0.61). In patients total, MCP-1 correlated with any HRCT finding and calcinosis (0.34 and 0.40); in active patients MCP-1 and calcinosis correlated (0.34). Eotaxin correlated with ILD in both patients total and active patients (0.37 and 0.38).

The following cytokines correlated with HRCT findings in inactive patients only; IL-17 with any HRCT findings and ILD (0.61 and 0.52), MIP1a with any HRCT findings (0.63) and IL-5 with ILD (-0.42).

Conclusion: In JDM, lung involvement was associated with mainly proinflammatory cytokines in active and profibrotic/proinflammatory cytokines in inactive patients. The association between higher eotaxin and better gas diffusion was interesting, since we have previously demonstrated an association between higher eotaxin and cardiac dysfunction (Ref 2).

REFERENCES:

- [1] Almeida, A&R 2015;67(9)
- [2] Schwartz, Rheumatology, 2014;53(12)

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OP0257

CHILDHOOD-ONSET MONOGENIC SYSTEMIC LUPUS ERYTHEMATOSUS NOT DUE TO COMPLEMENT DEFICIENCY: A SYSTEMATIC REVIEW OF 90 CASES

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Background: The paediatric SLE (pSLE) are estimated 10 to 17% of SLE (1). Studies comparing pSLE with adult-onset SLE reported high prevalence of pre-existing organ damage at diagnosis due to the diagnosis delay, more severe disease clinical course with high disease activity resulting in worse prognosis in pSLE (1,2). Recently, whole exome sequencing and next-gene sequencing have facilitated the identification of rare monogenic variants associated with SLE and lupus-like phenotypes with high penetrance (3,4)

Objectives: To reporting the whole spectrum of monogenic pSLE according to pathway abnormalities, using a meta-analysis (MA) approach.

Methods: A systematic review of studies focused on monogenic pSLE were analysed. To be included in the systematic review, studies had to meet simultaneously all the following criteria: (i) reported at least 1 case of SLE (ii) started before the age of 16 (iii) with clearly description of the diagnosis criteria and (iv) provided genetic data of the case.

We pooled the genes into three main groups of signalling pathways: (i) genes that affect adaptive immunity pathways including the lymphocyte apoptosis (FAS, KRAS, PTPN11, SHOC2) and the B and T cell development checkpoints (PRKCD, RAG2, IKZF1, DOCK8, WASP), (ii) genes containing type I interferon (IFN) pathways (ACP5, TREX1, SAMHD1, RNASEH2A, RNASEH2B, RNASEH2C, IFIH1, DNASE1L3, DNASE1, TMEM173, Tetrasomy 9), and (iii) metabolism pathways including both amino acid metabolism (PEPD, SLC7A7, MAN2B1) and oxidative metabolism (NCF2). Clinical and laboratory data were analysed according to the SLICC classification.

Fig 1: The PRISMA 2009 flow diagram of literature searched process for the study.

Results: We included 42 articles encompassing 88 patients, plus 2 additional unpublished cases of one author (AB). The MA process were carried out according to the PRISMA statement.

According to the SLICC classification, the blood disorders were significantly higher in the group of the metabolism pathway as well as the positivity of direct

Coombs test. The positivity of antibodies anti-Sm was also a distinguishing element for this group, while the positivity of ALP antibodies was the lonely manifestation to distinguish the adaptive immunity pathway from the others. Fever, recurrent infections, hepatosplenomegaly, and pulmonary diseases were significantly predominant in the metabolism pathways. In the group of the IFN pathway, the most distinctive criteria were the neurological manifestations and bone changes. There were no statistically significant differences in all groups concerning all other clinical or immunological criteria.

Conclusion: This is the first quantitative analysis of multiples cases reports, comparing the whole spectrum of monogenic pSLE according to three different pathways. Our results suggest that abnormalities in signaling pathway delimitate different SLE juvenile subset. The clinical and biological differing between the three signaling pathway were not specific, but our results may help to detect phenotypes requiring targeted genetic investigations. Subsets of SLE syndrome have to be identified to drive the treatment and propose personalized medicine.

REFERENCES:

- [1] Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. *Lupus*. 2011 Nov;20(13):1345–55.
- [2] Hedrich CM, Smith EMD, Beresford MW. Juvenile-onset systemic lupus erythematosus (jSLE) – Pathophysiological concepts and treatment options. *Best Pract Res Clin Rheumatol*. 2017 Aug;31(4):488–504.
- [3] Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2016 Dec;12(12):716–30.
- [4] Chung SA, Shum AK. Rare variants, autoimmune disease, and arthritis: *Curr Opin Rheumatol*. 2016 Jul;28(4):346–51.

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OP0258

LESSON FROM EUROFEVER REGISTRY AFTER THE FIRST TEN YEARS OF ENROLLMENT

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Background: In 2008 the Paediatric Rheumatology European Society (PReS) promoted an International Project for the study of Autoinflammatory Diseases (AIDs) named Eurofever, whose main purpose is to create a web-based registry for the collection of information in AIDs patients.

Objectives: To assess the impact of the Eurofever Registry on scientific community with particular interest in the geographical coverage, diagnostic delay, access to treatment and publications.

Methods: The data analyzed in the study were extracted from the Eurofever registry, which is hosted in the PRINTO website.

Results: Up to date 4175 patients have been enrolled from 62 countries (3843 of them with complete demographic data). Most of patients (72%) are resident in Western Europe, 8% in Central-Eastern Europe, 11% in Southern-Eastern Mediterranean, 2% in South America and 7% in other countries. Compared to the first Eurofever report (Toplak et al, 2012) we have observed an increase of enrolled patients from 1388 to 2651 in Western Europe, from 106 to 313 in Central-Eastern Europe, from 294 to 406 in Southern-Eastern Mediterranean. The median onset age is 4 years (range 1 month – 75 years), the median diagnosis age is 8 years (range 1 month – 78 years). The median diagnostic delay observed in 2012 was 7.3 years (range 0.3–76), from patients enrolled after 2012 it was 1.9 years (range 0–57). Comparing the mean diagnostic delay from 1980 to 2018, we have observed an encouraging constant reduction of period between AIDs onset e diagnosis (from a mean diagnostic delay value of 20 years for patients born before 1980, to a mean value of 1 year for patients born after 2011, Figure 1). Complete information on access to treatment were available in 2430 patients. DMARDs were used in 1031 (42%), biologics in 396 (16%) patients. According to the number of enrolled patients, biologics were used in 361/1782 (20%) of Western Europeans, 17/342 (5%) of Central-Eastern Europeans, 6/259 (2%) of Southern-Eastern Mediterranean patients. Regarding Eurofever impact on Scientific Community, during this first 10 years the Registry provided 12 papers with more than 800 citations. Detailed analysis of clinical features collected in Eurofever database allowed to perform studies with large cohort of patients, to purpose new classification criteria (Federici et al, 2015), to validate damage and activity score (Piram et