Disclosure of Interests: Soraia Azevedo: None declared, José Tavares-Costa: None declared, Ana Teresa Melo: None declared, Raquel Freitas: None declared, Marta Cabral: None declared, Marta Conde: None declared, Francisca Aguiar: None declared, Agna Neto: None declared, Ana Filipa Mourão: None declared, Filipa Oliveira-Ramos: None declared, Maria Jose Santos Speakers bureau: Novartis and Pfizer, Daniela Peixoto: None declared
DOI: 10.1136/annrheumdis-2020-eular.667

FRI0463

IDENTIFICATION OF EARLY CLINICAL AND LABORATORY CHARACTERISTICS OF MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Background: Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of systemic juvenile idiopathic arthritis (SJIA). However, early recognition of MAS remains challenging. Because it is clinically heterogeneous, hemophagocytosis is often not detected, and histopathological features lack the specificity associated with hemophagocytic syndromes. In addition, it is often difficult to distinguish early MAS from SJIA or sepsis-like syndromes.

Objectives: To identify early clinical and laboratory characteristics of MAS associated with SJIA.

Methods: This is a retrospective cohort study of 149 SJIA patients treated at the Children's Hospital of Zhejiang University School of Medicine between January 2010 to December 2017. All patients fulfilled 2001 ILAR criteria for SJIA, and 27 fulfilled 2016 Classification Criteria for MAS. We evaluated the clinical and laboratory features of SJIA patients with MAS and compared them to those without MAS. We focused our analysis on early MAS, which was defined as the time when the initial clinical and/or laboratory abnormalities suggestive of MAS were first detected.

Results: The clinical features associated with early MAS were hypotension, absence of arthritis and lymphadenopathy, bone marrow hemophagocytosis, central nervous system dysfunction, and gastrointestinal involvement. The best laboratory parameters for early MAS detection were platelet counts $\leq 275.0 \times 10^9/L$, lactate dehydrogenase $>596.0 U/L$, aspartate aminotransferase $>47.0 U/L$, erythrocyte sedimentation rates $\leq 41.0 mm/h$, ferritin $>1400.0 ng/mL$, D-dimer $>1.40 ng/mL$, triglyceride $>1.30 mmol/L$, alanine aminotransferase $>33.0 U/L$, C-reactive protein $\leq 68.0 mg/L$, fibrinogen $\leq 4.1 g/L$, absolute neutrophil counts $\leq 5.2 \times 10^9/L$, serum total protein $\leq 66.0 g/L$, and white blood cell $\leq 9.8 \times 10^9/L$. The combination of cytokines of IFN- $\gamma >17.1 pg/mL$ and IL-10 $>7.8 pg/mL$ were found to be a specific and good prognostic cytokine pattern for early recognition of MAS, the sensitivity and specificity as 71.4% and 98.2% (Table 1, Fig 1, 2).

Table 1. Identification of clinical and Cytokine characteristics differentiating patients with MAS onset from SJIA patients without MAS

Characteristics	Sensitivity (%)	Specificity (%)	OR (95% CI)	p value
Clinical characteristics				
Hypotension	35.5	98.4	33.0 (6.8–160.1)	0.000
Absence of Arthritis	77.4	85.2	19.8 (7.4–52.7)	0.000
Hemophagocytosis in the bone marrow	28.6	97.3	14.5 (2.0–107.5)	0.009
Central nervous system involvement	25.8	91.0	3.5 (1.3–9.7)	0.015
Gastrointestinal involvement	22.6	91.8	3.3 (1.1–9.4)	0.029
Absence of lymphadenopathy	77.4	51.6	2.6 (1.1–6.1)	0.027
Cytokine levels				
IFN- $\gamma >17.1 pg/mL$	82.1	83.6	49.5 (15.6–156.9)	0.000
IL-10 $>7.8 pg/mL$	78.6	93.1	23.5 (7.9–69.5)	0.000
IFN- $\gamma >17.1 pg/mL$ and IL-10 $>7.8 pg/mL$	71.4	98.2	142.5 (28.2–720.6)	0.000

OR, odds ratio. CI, confidence interval. PLT, platelet. LDH, lactate dehydrogenase. AST, aspartate aminotransferase. ESR, erythrocyte sedimentation rate. FER, ferritin. D-D, D-dimer. TG, triglycerides. ALT, alanine aminotransferase. CRP, C-reactive protein. FIB, fibrinogen. ANC, absolute neutrophil count; TP, total protein. WBC, white blood cells. ALB, albumin. IL, interleukin. IFN, interferon.

Fig 1. Comparison of clinical characteristics in the MAS process. * $P < 0.05$. ** $P < 0.01$. CNS involvement: Central nervous system involvement.

Fig 2. Comparison of serum cytokine levels in the MAS process. * $P < 0.05$. ** $P < 0.01$.

Conclusion: Sudden hypotension, absence of arthritis, and significantly increased IFN- γ and IL-10 levels are important clinical and laboratory markers for early MAS identification in addition to the traditional features of SJIA-associated MAS.

References: (not show references here)

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.1142

FRI0464

GENOTYPING AND PHENOTYPING PATTERNS IN PATIENTS WITH CAPS IN RUSSIAN FEDERATION

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Background: Cryopyrine-associated periodic syndromes (CAPS) are a group of rare congenital auto-inflammatory diseases (AID) that include diseases such as familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and CINCA/NOMID syndrome. At present, there are limited data on demographic and clinical features of children with CAPS in Russia.

Objectives: To reveal demographic, genotype and phenotype characteristics in CAPS patients at the National Medical Research Center of Children's health, Moscow, Russia.

Methods: Retrospective study included 12 patients (7 females, 58.3%) with CAPS confirmed by next generation sequencing (NGS). Median age of disease onset was 5.7 (interquartile range (IQR) 0.5:12.8) years. Characteristics of disease onset as well as dynamics of disease activity during long-term treatment were evaluated.

Results: At the onset, systemic features were as follows: fever in 11 (91.6%) patients, rash in 8 (66.7%), hepatosplenomegaly in 7 (58.3%) patients, and lymphadenopathy in 6 (50%). Active arthritis in the onset of the disease was in 9/12

patients (75%), presented by polyarthritis in 7/9 (77.8%), and oligoarthritis in 2/9 (22.2%). Two patients (16.7%) had cataract, one (8.3%) had bilateral uveitis, and one (8.3%) had optic atrophy. Sensorineural hearing loss was observed only in 3/12 (25%). Hydrocephalus was detected in 3/12 (25%). Delayed mental and psycho-speech development was observed in 6/12 (50%) patients. In 3/12 (25%), the development of MAS was recorded.

All patients had nucleotide variants in *NLRP3* gene. According to NGS results and clinical characteristics, 8/12 (66.7%) patients were diagnosed with MWS and 4/12 (33.3%) had CINCA/NOMID syndrome. In children with MWS, heterozygous variant c.2113C>A in *NLRP3* gene was the most common (5/8 (62.5%) patients). One of 8 (12.5%) patients with novel heterozygous variant c.2861C>T was detected; also one child (12.5%) have heterozygous variant c.598G>A and one (12.5%) – heterozygous variant c.943A>G. Four patients with CINCA/NOMID syndrome also had heterozygous variants in *NLRP3* gene: c.598G>A, c.2173C>A, c.1991T>C and c.796C>T.

Prior to genetic testing, 12/12 (100%) patients received NSAIDs; 6/12 (50%) were treated with oral glucocorticoids (GC), 3/12 (25%) – with intravenous GC, 2/12 (22.2%) – with methotrexate. Biologics treatment included: 5/12 (41.7%) CAN, 4/12 (33.3%) tocilizumab, and 1/12 (8.3%) etanercept. After genetic testing, 7/12 (58.3%) patients were successfully switched to CAN. Only 1/12 (8.3%) child with MWS developed secondary inefficiency on CAN treatment.

Conclusion: Systemic manifestations were detected in 91.6% of children, while active arthritis was observed in 75% of patients, which can cause difficulties in the diagnosis and treatment of CAPS. The effectiveness of canakinumab therapy was estimated in 91.6% of patients. The most frequent variant of the *NLRP3* gene in MWS was c.2113C>A. In patients with CINCA/NOMID syndrome all nucleotide variants were individual.

Disclosure of Interests: Meyri Shingarov: None declared, Ekaterina Alexeeva Grant/research support from: Roche, Pfizer, Centocor, Novartis, Speakers bureau: Roche, Novartis, Pfizer., Tatyana Dvoryakovskaya: None declared, Kirill Savostyanov: None declared, Aleksander Pushkov: None declared, Evgeniya Chistyakova: None declared, Ksenia Isaeva: None declared, Aleksandra Chomakhidze: None declared, Olga Lomakina: None declared, Rina Denisova: None declared, Anna Mamutova: None declared, Anna Fetisova: None declared, Marina Gautier: None declared, Dariya Vankova: None declared, Elizaveta Krekhova: None declared, Ivan Kriulin: None declared, Natalia Zhurkova: None declared, Rustam Tepaev: None declared, Alina Alshevskaya: None declared, Andrey Moskalev: None declared

DOI: 10.1136/annrheumdis-2020-eular.5814

FRI0465 TOFACITINIB POPULATION PHARMACOKINETICS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS: A POOLED ANALYSIS OF DATA FROM THREE CLINICAL STUDIES

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Background: Tofacitinib is an oral JAK inhibitor that is being investigated for juvenile idiopathic arthritis (JIA).

Objectives: To describe tofacitinib pharmacokinetics (PK) in patients with JIA, identify potential covariates accounting for variability in exposure, assess the formulation effect of oral solution vs tablet and propose a simplified dosing regimen.

Methods: This was a pooled analysis of data from 3 tofacitinib clinical studies in patients with JIA aged 2–<18 years: a Phase 1, open-label (OL), non-randomised study (NCT01513902); a Phase 3, randomised, double-blind, placebo-controlled, withdrawal study (NCT02592434); and an OL long-term extension study (NCT01500551). Tofacitinib was dosed at 5 mg twice daily (BID) in patients ≥40 kg or at body weight (BW)-based lower doses BID in patients <40 kg, to achieve average concentrations (C_{avg}) comparable with those in patients receiving 5 mg BID. A sparse PK sampling scheme was applied, and the plasma samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (lower limit of quantification = 0.100 ng/mL). A nonlinear mixed-effects modelling approach was used for the population PK model, and population parameter variability was assumed to be log-normally distributed. Covariates relating to patient demographics, disease characteristics, concomitant medications and formulation (oral solution vs tablet) were selected using a stepwise covariate modelling approach, and parameter-covariate relationships were evaluated using stepwise forward-inclusion ($p < 0.05$) backward-deletion ($p < 0.001$) procedures. The effect of time-varying BW on oral clearance (CL/F) and apparent volume of distribution (V/F) was characterised using an allometric model. Final model quality was assessed by Visual Predictive Checks (VPCs).

Results: Of 246 patients in the analysis, 74.0% were female; 87.8% were white, 2% were black, 10.2% were 'other' races and no patients were Asian. Median (range)

BW was 46.3 (11.1–121.8) kg. Initially, 100 patients received oral solution and 146 patients received tablets; 11 patients switched formulations during the studies. A one compartment disposition model with first-order absorption and a lag time sufficiently described the data. Final estimates for CL/F, V/F and the first-order absorption rate constant (k_a) for tablets were 26.1 L/hr, 89.2 L and 2.78 hr⁻¹, respectively. The only statistically significant covariate was a formulation effect on k_a . All parameters were estimated adequately. Estimated allometric exponents were 0.310 for CL/F and 0.537 for V/F. Absorption was described with an estimated lag time of 0.186 hr, and the oral solution had a 1.64-fold faster absorption rate vs the tablet. VPCs sufficiently described the observed data over time, across BWs and ages. Given the PK characterisation and variability in patients with JIA, a simplified dosing scheme was proposed, targeting C_{avg} values equivalent to those in patients receiving 5 mg BID: 3.2 mg BID solution in patients 10–<20 kg; 4 mg BID solution in patients 20–<40 kg; and 5 mg BID tablet or solution in patients ≥40 kg.

Conclusion: Tofacitinib population PK in patients with JIA were adequately described by a one compartment model parameterised in terms of CL/F, V/F and first-order absorption with a lag time. Drug absorption from the oral solution was faster than from the tablet. Tofacitinib does not require dose modification or restrictions for any covariates, except BW, to account for differences in C_{avg} . Based on the results of this analysis, a simplified BW-based dosing regimen was proposed.

Acknowledgments: Study sponsored by Pfizer Inc. Medical writing support was provided by Sarah Piggott of CMC Connect and funded by Pfizer Inc.

Disclosure of Interests: Camille Vong Shareholder of: Pfizer Inc, at time of analysis, Employee of: Pfizer Inc, at time of analysis, Xiaoxing Wang Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Anasuya Hazra Shareholder of: Pfizer Inc, at time of analysis, Employee of: Pfizer Inc, at time of analysis, Arnab Mukherjee Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Timothy Nicholas Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Cheng Chang Shareholder of: Pfizer Inc, Employee of: Pfizer Inc

DOI: 10.1136/annrheumdis-2020-eular.400

FRI0466

NO DISEASE PROGRESSION AFTER 36 MONTHS FOLLOW UP IN THE JUVENILE SYSTEMIC SCLERODERMA INCEPTION COHORT

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Background: Juvenile systemic sclerosis (JSSc) is an orphan disease with a prevalence of 3 in 1 000 000 children. There is rare longitudinal prospective follow up data of patients with JSSc. In the international juvenile systemic sclerosis cohort (JSScC) patients are followed with a standardized assessment prospectively.

Objectives: To assess the changes regarding organ involvement pattern and patients related outcomes after 36 months follow up in the JSScC.

Methods: Patients diagnosed according to the ACR 2013 criteria for systemic sclerosis were included, if they developed the first non-Raynaud symptom before the age of 16 and were under the age of 18 at the time of inclusion. Patients were followed prospectively every 6 months with a standardized assessment.

Results: 39 patients in the JSScC had 36 months follow up. 80% had a diffuse subtype. 95% of the patients were Caucasian origin. 31 of the patients were female (80%). Mean disease duration at time of inclusion was 3.5 years. Mean age onset of Raynaud's was 8.8 years and mean age of onset at the first non-Raynaud's was 9.5 years. Around 30% of the patients were anti-Scl70 positive and none of them anti-centromere positive. The MRSS dropped from the time point of the inclusion into the cohort from 13.9 to 11.8 after 36 months. Pattern of organ involvement did not show any significant change, beside the increase of the nailfold capillary changes from 49% to 73% ($p = 0.037$). No renal crisis occurred. No mortality was observed.

They were positive significant changes in the patient related outcomes. The physician global disease activity decreased from 40.0 to 22.1 assessed on a VAS scale of 0 to 100 ($p < 0.001$).

Patients global disease activity decreased from 43.3 to 20.4 and patients global disease damage from 45.0 to 21.7 both assessed on a VAS scale of 0 to 100 ($p < 0.001$).

Conclusion: After 36 months follow up, we could observe a significant improvement of patient related outcomes and only one significant change in organ pattern involvement. In a mostly diffuse subset patient population this is a very promising result regarding outcome.

Supported by the "Joachim Herz Stiftung"

Disclosure of Interests: Ivan Foeldvari Consultant of: Novartis, Jens Klotzsche: None declared, Ozgur Kasapcopur: None declared, Amra Adrovic: None