### Table 1. Baseline characteristics and 4th interim analysis data of patients with FMF

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>24 months</th>
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</thead>
<tbody>
<tr>
<td>Number of patients, N</td>
<td>74</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Number (%) of patients with days absent from work/school during last 6 months</td>
<td>6 (8)</td>
<td>11 (24)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Number (%) of patients in disease remission (physician assessment)</td>
<td>22 (45)</td>
<td>23 (72)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Patient's assessment of current disease activity: 0–10, (median; min; max)</td>
<td>2.0 (0; 10)</td>
<td>2.0 (0; 7)</td>
<td>2.0 (0; 10)</td>
</tr>
<tr>
<td>Patient's assessment of current fatigue; 0–10, (median; min; max)</td>
<td>5.0 (0; 10)</td>
<td>4.0 (0; 10)</td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients without impairment of social life by the disease</td>
<td>27 (50)</td>
<td>28 (80)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>CRP (mg/dl) / SAA (mg/dl) / ESR (mm/h); median; IQR</td>
<td>0.2 (0.7) / 1.8</td>
<td>0.2 (0.5) / 4.0</td>
<td>0.2 (0.7) / 6.0</td>
</tr>
<tr>
<td>Number (%) of patients with disease-related symptoms prior to inclusion</td>
<td>12 months</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>Number of events</td>
<td>Incidence rate/100 patient years</td>
<td></td>
</tr>
<tr>
<td>All types of SAE</td>
<td>18</td>
<td>14.03</td>
<td></td>
</tr>
<tr>
<td>SADR</td>
<td>2</td>
<td>1.56</td>
<td></td>
</tr>
</tbody>
</table>

Incidence rate = number of events / 36,525 / sum of observation days. (-48,848); CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; n: n.; not annotated; SAA: serum amyloid A; SADR, serious adverse drug reaction; SAE, serious adverse events.

### Conclusion: Interim data of FMF patients from the RELIANCE study, the longest running real-life canakinumab registry confirm efficacy and safety of long-term canakinumab treatment.

### REFERENCES:


### Discourse of Interests: Jörg Henes Consultant of:Novartis, AbbVie, Sobi, Roche, Janssens, Boehringer-Ingelheim, Grant/research support from: Novartis, AbbVie, J. B. Kueemmerle-Dechear Consultant of:Novartis, AbbVie, Sobi, Roche, Janssens, Boehringer-Ingelheim, Grant/research support from: Novartis, AbbVie, Sobi, Tobias Krickau Speaks to: Novartis, Consultant of: Novartis, Consultant of: Novartis, AbbVie, Roche, Grant/research support from: Novartis, Tilmann Kaellinich Consultant of: Novartis, AbbVie, Roche, Grant/research support from: Novartis, Frank Dressler Consultant of: AbbVie, Mylan, Novartis, Pfizer, Grant/research support from: Novartis, Gerhard Hornfress: Speaks to: Novartis, Bayer, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Grant/research support from: AbbVie, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Florian Meier Speakers bureau: Novartis, Ivan Foevelsdorff Consultant of: Novartis, AbbVie, Roche, Hael, Medac, Pfizer, Frank Weller-Heinemann: None declared, Birgit Kortus-Goetze Consultant of: Novartis, Markus Hufnagel Consultant of: Novartis, Jürgen Rech Consultants Bureau: AbbVie, Biogen, BMS, Chugai, GSK, Janssens, Lilly, MSD, Mylan, Novartis, Roche, Sandoz, Sobi, UCB, Grant/research support from: Novartis, Sobi, Prasad Komarneni Consultant/research support from: Novartis, Julia Weber-Arden Consultant of: Novartis, Norbert Blank Consultant of: Novartis, Sobi, Lilly, Pfizer, AbbVie, BMS, MSD, Actelion, UCB, Boehringer-Ingelheim, Roche, Sobi, Grant/research support from: Novartis, Sobi, DOI: 10.1136/annrheumdis-2022-eular.4839

### OP0043

**TOCILIZUMAB SIGNIFICANTLY REDUCES SERUM AMYLOID A IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER – DATA FROM THE PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND TOFFIFE STUDY**

J. Henes1, S. Saur2, D. M. Koller3, C. Kedir4, C. Meisner5, M. Krusche6, I. Köter7, T. Xenidis1, H. Schulze-Koops1, E. Feist1, 1University Hospital Tübingen, Centre for Interdisciplinary Clinical Immunology, Rheumatology and Auto-inflammatory Diseases and Department of Internal Medicine II (Oncology, Haematology, Immunology and Rheumatology), Tübingen, Germany; 2University Hospital Cologne, Division of Rheumatology and Clinical Immunology, Department I of Internal Medicine, Cologne, Germany; 3Charité-Universitätsmedizin Berlin, Institute of Medical Immunology, Berlin, Germany; 4Robert Bosch Hospital, Study Center, Stuttgart, Germany; 5University Hospital Hamburg Eppendorf, Division of Rheumatology and Systemic Inflammatory Diseases, Hamburg, Germany; 6University of Munich, Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, Munich, Germany; 7Helios Fachklinik Vogelsang-Gommern, Department of Rheumatology, Vogelsang-Gommern, Germany

**Background:** Uncontrolled inflammation in patients with familial Mediterranean fever (FMF) can lead to severe organ failure due to amyloidosis. Colchicine is still the standard treatment and the only therapy that has been proven to reduce the risk for amyloidosis. Besides colchicine the Interleukin (IL)-1-antagonists Anakinra and Canakinumab are approved, but new treatment options are still needed. The IL-6 antagonist Tocilizumab (TCZ) effectively reduces inflammation and is approved in several other rheumatic indication. Here we present data from our phase II study TCZ for the treatment of FMF – TOFFIFE.

**Objectives:** To explore the efficacy and safety of tocilizumab in FMF.

**Methods:** The TOFFIFE study was a placebo-controlled, double-blinded, randomized trial to investigate the efficacy and safety of TCZ in patients with colchicine resistant (cr)FMF. The physician's global assessment of disease activity (PGA) based on a 5 point-scale for 6 symptoms (range 0-24) was used as a clinical score and had to be ≤2 at screening. Patients were randomized 1:1 to either receive monthly TCZ intravenously with 8 mg/kg bodyweight or placebo over a period of 24 weeks. Patients with inadequate response after week 12 had the opportunity to receive open label TCZ at week 16. The primary endpoint was the number of patients achieving an adequate response to treatment at week 16, defined as a PGA ≤ 2 + normalized ESR or CRP (the item that led to inclusion had to be normalized) + normalized SAA. Secondary endpoints included normalization of SAA during treatment and safety of TCZ in FMF patients.

**Results:** 25 patients were randomized with a median age of 31 years (range 18 - 53y), of which 14 (56%) were female. At week 16, which was the timepoint for the primary end point, 2 (15.4%) patients in the TCZ arm reached the primary end point with a PGA ≤ 2 and normalization of SAA and ESR and/or CRP but none of the patients in the placebo arm. Therefore, the superiority of TCZ compared to placebo could be shown concerning the pre-specified significance level of α = 0.05 (p = 0.089). SAA levels normalized with TCZ but not with PBO. This difference between TCZ and PBO was highly significant; SAA p < 0.005. At week 28 with 17 remaining patients and after having had the opportunity for a rescue treatment at week 16, the responder rates (PGA ≤ 2 + normalization of SAA, ESR and/or CRP) were 25% (n=1) in those patients who changed from placebo to TCZ (n=4) and 20% (n=2) in those patients who continued with TCZ (n=10). Of note, all 3 patients remaining on PBO were non-responders (p = 0.842). In 75% of patients (n=3) CRP and in 50% SAA (n=2) normalized after changing to TCZ. No new safety aspects occurred.

**Conclusion:** In this first randomized, placebo-controlled study in patients with active crFMF TCZ significantly reduced and normalized SAA levels. The trial met the primary endpoint to demonstrate the superiority of TCZ over PBO although only a small numerical difference was found. Nevertheless, the proportion of patients with a successful TCZ-therapy was lower than expected due to very strict response criteria; patients had to achieve a complete remission with a PGA ≤ 2 (on a 0-24 scale) and normalization of the inflammatory parameters (CRP/ESR and SAA). This required no or only mildest symptoms during the last 4 weeks. A larger multicenter study is therefore justifiable and needs to clarify the benefit of TCZ treatment in FMF.

**Figure 1.** Secondary endpoint: Serum Amyloid A over time, showing a clear reduction in the TCZ but not in the PBO arm and rise of SAA after discontinuation after week 28. Normal SAA value = < 10mg/l. Outliers > 100mg/l were excluded in this graph.
Disclosure of Interests: Jörg Henes Speakers bureau: SOBI, Novartis, Roche/Chugai, Consultant of: SOBI, Novartis, Roche/Chugai, Grant/research support from: SOBI, Novartis, Roche/Chugai, Sebastian Saur: None declared, Christoph Meisner: None declared, Martin Krusche: None declared, Christoph Meisner: None declared, Martin Krusche: None declared, Hendrik Schulze-Koops Speakers bureau: SOBI, Novartis, Roche/Chugai, Ina Kött Speakers bureau: SOBI, Novartis, Roche/Chugai, Consultant of: SOBI, Novartis, Roche/Chugai, Theodoros Xentidis: None declared, Hendrik Schulze-Koops: None declared

In these patients. γ

provided suggesting that IFN-

Conclusion: that 3477 among type I, II, and III IFN-related genes (IRGs) were significantly different in AOSD synovial tissues. Finally, the transcriptomic profile, by RNA-sequencing analysis, showed

Results: in patients with IRP. Trial registra-

α

Background: Adult-onset Still's disease (AOSD) is a rare multicentric autoinflammatory disease of unknown aetiology burdened by life-threatening, such as macrophage activation syndrome (MAS) [1]. Considering the poor outcome of MAS patients, previous works tried to assess predictive factors of its occurrence during AOSD [2-4]. However, an integrated evaluation of clinical features with biomolecules, not reflecting the pathogenetic mechanisms of the disease and its complications, is still missing.

Objectives: To multidimensionally characterise MAS complicating AOSD considering cytokine profile, inflammatory markers, and multi-visceral involvement of the disease. To perform a high-dimensional phenotypic analysis of circulating immune cells in AOSD patients with and without MAS. To assess interferon (INF)-related pathways in AOSD synovial tissues by a bulky RNA sequencing. Methods: To multidimensionally compare AOSD patients with or without MAS, considering cytokine profile, inflammatory markers, and multi-visceral involvement of the disease. Clinical and biologic data were collected and compared in AOSD patients with and without MAS. Sera biomolecules were analysed by Luminex multiplexing technology. Mass cytometry (CyTOF) was used to characterise circulating immune cells. A bulky RNA sequencing was performed in AOSD synovial tissues.

Results: In this study, 40 consecutive AOSD patients (42.7±15.0 years, 50.0% male gender) were assessed at the time of diagnosis before the administration of any immunosuppressive therapy. Out of those, 14 (35%) patients were complicated by MAS. Paralleling with increases of systemic score and ferritin, MAS patients were characterised by an increased concentration of IL-1α, IL-1β, IL-1Ra, IL-2Ra, IL-6, IL-17A, IFN-γ, G-CSF, MCF-1, MIP-1α, SCF. Among these biomolecules, IL-1Ra, IFN-γ, MCF-1, and SCF were correlated with MAS. Considering the discriminatory ability of these data in identifying MAS, the best model was composed by systemic score, ferritin, IFN-γ, and IL-10. This model was characterised by AUC=0.99 (Standard error: 0.008; 95%CI: 0.976–1.000), sensitivity=100%, specificity=95.45%. By CyTOF analysis, AOSD patients, who were complicated by MAS were characterised by a significant increase of circulating "clasical monocytes" (CD14+CD34+). MAS patients were characterised by a significant reduction of NK cells (CD45R+CD56dim) than AOSD patients. Finally, the transcriptomic profile, by RNA-sequencing analysis, showed that 3477 among type I, II, and III IFN-related genes (IRGs) were significantly different in AOSD synovial tissues.

Conclusion: A multidimensional characterisation of AOSD patients was provided suggesting that IFN-γ, IL-10, ferritin, and systemic score discriminated MAS, thus identifying the occurrence of the cytokine storm syndrome. The inflammatory milieu of AOSD and MAS may be associated with a signature of circulating immune cells. Finally, our results about IRGs reinforced the role of IFN-γ in these patients.

REFERENCES:


Disclosures of Interests: Martin Krusche Speakers bureau: SOBI, Novartis, Roche/Chugai, Consultant of: SOBI, Novartis, Roche/Chugai, Grant/research support from: SOBI, Novartis, Roche/Chugai, Sebastian Saur: None declared, Christoph Meisner: None declared, Martin Krusche: None declared, Hendrik Schulze-Koops: None declared.