Title: Comparative study of Interleukin-18 (IL-18) Serum levels in Adult Onset Still's Disease (AOSD) and Systemic Onset Juvenile Idiopathic Arthritis (sJIA) and its use as a Biomarker for Diagnosis and Evaluation of Disease Activity.

Version: 0 Date: 03 May 2018

Reviewer: Lovro Lamot

Reviewer's report:

This is very interesting study investigating the levels of IL-18 in patients with adult and childhood onset systemic arthritis, and comparing them to group of patients with other rheumatic diseases. The cohort of patients included in this study is remarkable and statistical methods are well chosen, while the results of this study gives added value to growing number of studies which highlights IL-18 as an important biomarker in systemic arthritis, that can remain elevated for more than six months despite treatment.

Nevertheless, there are some concerns regarding definition of groups of participants involved in this study as well as criteria for remission.

1. In the AOSD group only 20 of 30 patients met Yamaguchi criteria. I recommend further clarifications for the patients who did not met the criteria, but were involved in the study. Since both ILAR and Yamaguchi criteria were used for sJIA patients, I also suggest the use of ILAR criteria in adult patients, which could lead to some interesting conclusions, as in recently published paper (Yang et al. Application of the international league against rheumatism classification criteria for systemic juvenile idiopathic arthritis as a prognostic factor in patients with adults-onset Still's disease. Pediatr Rheumatol Online J. 2018 Jan 25;16(1):9. doi: 10.1186/s12969-018-0225-1).

2. My biggest concerns are directed towards criteria used in sJIA group. Although it is well known that patients in sJIA often don't have arthritis for more than 6 weeks, as demanded by ILAR criteria, they should have fever. In a very recent paper from Germany (Hinze et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J. 2018; 16: 7. doi: 10.1186/s12969-018-0224-2) it is stated that 97,6% of patients diagnosed with sJIA within German AID registry had fever and 59,9% had arthritis. Also, it is not clear how the diagnosis was made in patients who did not meet any of the criteria, and although in AOSD group it is stated that diagnosis was made by experienced rheumatologists, it is not clear it
the diagnosis of sJIA was made by pediatric rheumatologists. Therefore, I recommend extensive clarification of the criteria used to reach diagnosis in this group of patients.

3. I also have concerns regarding the control group. It is stated that in control groups there was 65 adults with 48 different rheumatic diseases and 23 children with 22 different rheumatic and/or inflammatory diseases. These statements draw me to conclusion that almost all of the patients had different rheumatic disease; if this is true, I recommend to cluster those patients in similar disease groups (e.g. periodic fevers, interferonopathies etc).

4. I also suggest giving more details on the treatment used for patients with AOSD and sJIA (e.g. how many was treated with biologics).

5. My final concern is directed towards disease remission criteria. Although Rau score is well elaborated in the manuscript, I was not able to find any other paper in which Rau score was used to define remission in sJIA patients. Therefore, I suggest use of at least partially verified criteria for inactive disease, such are JADAS10 criteria (Hinze et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J. 2018; 16: 7. doi: 10.1186/s12969-018-0224-2).

Finally, this study has a lot of potential, primarily due to a large cohort, and it is my strong opinion it should be published after necessary adjustments are made.

I also suggest proof reading of the article in order to improve scientific English.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

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