Author’s response to reviews

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.

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Author’s response to reviews:

Response letter

Dear Editors,

This is to resubmit the enclosed manuscript entitled “First retrospective noninterventional 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” as research article.

First of all, I would like to thank the reviewers for their constructive comments. I would like to address the comments made by the reviewers starting with reviewer one:

1. I included how many of the AOSD patients would have met the ILAR criteria if used in adult patients. (line 133-135). Further conclusions cannot be drawn due to the small number of patients. I am in doubt if any comparison between ILAR classification criteria for sJIA and AOSD classification are useful. The ILAR criteria require arthritis of one or more joints as mandatory symptom [1]. In German registries only around 60% of sJIA patients had arthritis [2] just as in AOSD. The cited work by Yang et al. [3] interpreted the ILAR classification criteria for sJIA [1] in a different way. The authors said that patients with fever or arthritis met the requirement for the ILAR classification. This is misleading and wrong.
conclusions are drawn. Since we interpreted the ILAR classification criteria in its original way we had only few AOSD patients that met the used AOSD and ILAR classification criteria. Therefore, a comparison between both classification criteria was not made and was not aim of the study.

2. I agree with the concerns about the definite diagnosis of AOSD and sJIA but our study is a retrospective study with all its disadvantages. We had to rely on the diagnoses made. Other diagnoses had to be ruled out. We checked the diagnosis made and retained it when clinically sound. Corresponding changes are made in the original paper lines 136/137 and 176-178. Not all patients had active disease when IL-18 samples were taken, so not all patients could meet the classification criteria at this point of time. As mentioned earlier the ILAR criteria [1] formally require six weeks of arthritis and fever to meet the classification criteria. Even in the current literature the ILAR criteria seem “unrealistic in the real world since most patients require treatment much earlier” [2]. Having this in mind it is not a surprise that only 11 of 20 patients with sJIA in our study met the ILAR criteria. This reflects the finding of the AID registry and the ICON-JIA cohort identifying only 47.8 and 54.3% of the patients with sJIA when applying the criteria de facto [2], what we did. A comment is added in the paper in lines 181-184. As stated by Dr. Lamot almost all of patients diagnosed with sJIA have fever. In our sJIA children’s cohort with active disease 100% had fever which is in concordance with the German AID registry and ICON-JIA cohort. To show this I attached another table with clinical characteristics of active sJIA to the manuscript (additional file: table S 3: clinical characteristics of active sJIA) and added a statement in lines 184-186.

3. Regarding the control group it is true that almost all of the patients had different rheumatic or other diseases. For further clarification I attached two more tables with a list of diseases in the adult control group and a list of diseases in children’s control group (additional file: Table S 1: List of diagnoses in adult control group; Table S 2: List of diseases in children’s control group). Because of the wide range of diagnoses made and most of them only appearing once it is not rational for statistical reasons to try to cluster them in disease groups. A change in the manuscript was made in line 100.

4. Regarding treatment of the patients I added additional information in lines 137-142 for AOSD and in lines 186-189 for sJIA.

5. Regarding remission criteria. As mentioned earlier it is a retrospective study. Not all parameters that would have been necessary to use the JADAS [4] or the Wallace criteria [5] were available. Especially the very subjective physician global assessment score and parent or patient global assessment score were not available in the clinical daily life records. The parameters for Rau’s Score [6] were available and therefore used for adults and children for
better comparability. Furthermore, the JADAS[4] is of limited use since one fourth of the score is based on an active joint count, knowing that in sJIA only few joints if at all are affected. Furthermore, we could not find widely accepted and used remission criteria for sJIA in the studies evaluating potential biomarkers. Even in more recent publications neither the JADAS nor the Wallace criteria were used (Brachat et al. [7], Inoue et al. [8]). Brachat et al. [7] used modified Wallace criteria. Adjustments to the manuscript were made in line 111-116.

Comment to reviewer two:

1. It is true that the use of IL-18 as potential biomarker for AOSD and sJIA is discussed for over 10 years. Until 2017 there was no bigger study that also measured IL-18 serum levels consecutively. The cited study of Brachat et al. [7] did not evaluate IL-18 as diagnostic biomarker but only as biomarker for disease activity. The longest observational period stated was 197 days. Until then they found no significant statistical difference in IL-18 serum levels in active and inactive disease [7] even though IL-18 serum levels were lower in inactive disease [7]. This does not mean that the reduction of IL-18 serum levels will not meet statistical significance if observed longer. It rather reflects, just as Jung et al. [9], our point of view that a persisting elevation of IL-18 serum levels is an expression of underlying subclinical disease activity. In our study two patients still showed clearly elevated IL-18 serum levels long after achieving remission (30 months) but showed a gradual normalization as described by Kawashima et al.[10]. Inoue et al. [8] had similar results as us. They even go further and propose different clinical subsets of AOSD and sJIA based on IL-18 and IL-6 levels [8]. Despite the reviewers opinion that the implementation of IL-18 as diagnostic biomarker and biomarker for disease activity is not realistic there is more and more evidence that it is accepted and used as biomarker in AOSD in a couple of more recent review articles [11–13]. In the context of a possible promising future therapy of AOSD with IL-18 binding protein (tadekinig alfa) [14] the implementation of IL-18 as a biomarker for AOSD should be aspired even stronger and any new studies on IL-18 in favor of or against its use as a biomarker in AOSD and sJIA should be published to have more reliable evidence. I added a small paragraph to the article including the study by Brachat et al. [7] (lines 274, 279-282).

In addition, I would like to state, that the article has been corrected for scientific English from a native speaker of our institution.

The article has not been published or is not under consideration for publication anywhere else.

The final manuscript has been read and approved by all of the authors.
We are looking forward to your kind consideration of the manuscript.

Sincerely,

Holger Kudela

References


