Response to: 'Correspondence on 'Changing the outcome measures, changing the results? The urgent need of a specific disease activity score to adult-onset Still's disease" by Muraviov and Muraviova

Dear Editor,

We read the correspondence by Muravion and Muravion[1] about our previous correspondence on a recent clinical trial investigating the efficacy of canakinumab on adult-onset Still's disease (AOSD)[2 3] with interest.

In this correspondence, Muravion and Muravion highlighted the role of disease activity score in 28 joints (DAS28) in assessing the disease activity in AOSD, also advocating American College of Rheumatology definitions of clinical response and treat-to-target recommendations.[1] This is relevant in the context of rheumatoid arthritis (RA). However, it is well recognised that AOSD is a different disease from RA, considering pathogenic mechanisms, clinical features and therapeutic strategies.[4 5]

Different from RA, AOSD-associated arthritis, usually an oligoarthritis, is present in two-thirds of these patients, migrating between joints at the very beginning and becoming stable within the course of the disease.[6] Although any joint might be affected, wrists, knees and ankles are frequently involved in AOSD arthritis. However, proximal interphalangeal and metacarpophalangeal joints of the hands and small joints of the feet, including the metatarsophalangeal joints, are scarcely affected in these patients.[6 7] Rarely, AOSD is characterised by symmetrical RA-like polyarthritis. This pattern of joint involvement does not fully justify the application of the DAS28 in AOSD. Furthermore, DAS28 does not entirely assess the systemic features of the disease. In fact, in previous studies, which are mentioned by Muravion and Muravion,[8 9] the clinical response has been defined combining DAS28 reduction and disappearance of fever in assessed patients.[8 9] In any case, the DAS28 is not validated for assessing AOSD disease activity so far; thus, it is not simply possible to translate its use in these patients based on evidence deriving from a different disease. The measures of outcome derived from RA do not fully evaluate the disease activity in AOSD, since these are characterised by the lack of comprehensiveness and responsiveness on these patients.

Furthermore, Muravion and Muravion suggested the use of systemic score as disease activity score.[1] The systemic score, proposed by Pouchot *et al*,[10] is designed as a severity score, and its sensitivity to change is not investigated so far. In a large cohort of patients with AOSD, one of the largest published in literature, the use of the systemic score has been validated as a prognostic tool, not as a disease activity score, identifying a subset of patients at higher risk of life-threatening complications and mortality.[11] In this context, some authors modified the systemic score to evaluate the activity of AOSD.[12] Despite its being closer to disease activity than other proposed measures, some variables, which are included in the score, are not clearly defined and could thus not be precisely measured.

As far as the strong rationale of inhibiting interleukin (IL)-1 in AOSD questioned by [1]Muravion and Muravion is concerned, multiple lines of evidence clearly reported the usefulness of biological disease-modifying antirheumatic drugs (DMARDs) targeting IL-1 in these patients.[13 14] The importance of inhibiting IL-1 is also confirmed by the possibility to change the natural history of the patients by an early administration during the first phases of the disease, as shown in the juvenile counterpart of AOSD.[15 16]

In conclusion, we still consider an urgent need the development of a validated disease activity score in AOSD. The lack of this clinical tool is also documented by the available clinical trials on AOSD, which developed their own criteria of response, consequently reducing the comparability and the reproducibility of obtained results.[3 17 18] Furthermore, the urgency of a validated disease activity score is suggested, since the therapeutic strategy in AOSD, including definition of refractory patients and choice of which class of biological DMARDs, is mainly related to the clinical judgement which combines scientific theory, but also personal clinical experience, patient perspectives and other insights.[19 20] However, with the rise of modern research methodology, the fallacious aspects of clinical judgement have been increasingly stressed, undertaking something like low-quality correlational statistics.[19 20] Thus, in the era of evidence-based and precision medicine, a validated score to accurately measure AOSD activity is of crucial importance to comprehensively investigate the disease, balancing appropriate therapy, minimising the exposure to iatrogenic harm and avoiding unnecessary expenditures. Conversely, the mere translation of evidence from another disease to AOSD might impair the management of these patients.

Piero Ruscitti,[1] Tanja A Stamm ,[2] Roberto Giacomelli [1]

[1]Department of Clinical Sciences and Applied Biotechnology, University of L'Aquila, L'Aquila, Abruzzo, Italy
[2]Section for Outcomes Research, Center for Medical Statistics, Informatics and Intelligent System, Medical University of Vienna, Vienna, Austria

Correspondence to Dr Roberto Giacomelli, University of L'Aquila Department of Clinical Sciences and Applied Biotechnology, L'Aquila, Abruzzo, Italy; roberto.giacomelli@cc.univaq.it

Handling editor Josef S Smolen

Contributors All the authors met all criteria for authorship in the ICMJE Recommendations, since all authors made substantial contributions to the conception or design of the work, the acquisition and interpretation of data. All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Ruscitti P, Stamm TA, Giacomelli R. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218868

Received 18 August 2020
Revised 19 August 2020
Accepted 20 August 2020

Linked

► https://doi.org/10.1136/annrheumdis-2020-218692

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218868

ORCID iDs
Tanja A Stamm http://orcid.org/0000-0003-3073-7284
Roberto Giacomelli http://orcid.org/0000-0003-0670-9638

REFERENCES

1 Muravion Y, Muravion L. Correspondence on "Changing the outcome measures, changing the results? The urgent need of a specific disease activity score to adult-onset Still's disease". *Ann Rheum Dis* 2020. doi: 10.1136/annrheumdis-2020-218692.
2 Ruscitti P, Stamm TA, Giacomelli R. Changing the outcome measures, changing the results? the urgent need of a specific disease activity score to adult-onset still's disease. *Ann Rheum Dis* 2020:annrheumdis-2020-218032.
3 Kedor C, Listing J, Zernicke J, *et al*. Canakinumab for treatment of adult-onset still's disease to achieve reduction of arthritic manifestation (consider): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis* 2020;79:1090–7.
4 Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset still's disease. *J Autoimmun* 2018;93:24–36.
5 Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset still's disease. *Nat Rev Rheumatol* 2018;14:603–18.
6 Fautrel B. Adult-Onset still disease. *Best Pract Res Clin Rheumatol* 2008;22:773–92.
7 Gerfaud-Valentin M, Jamilloux Y, Iwaz J, *et al*. Adult-Onset still's disease. *Autoimmun Rev* 2014;13:708–22.
8 Puéchal X, DeBandt M, Berthelot J-M, *et al*. Tocilizumab in refractory adult still's disease. *Arthritis Care Res* 2011;63:155–9.
9 Cipriani P, Ruscitti P, Carubbi F, *et al*. Tocilizumab for the treatment of adult-onset still's disease: results from a case series. *Clin Rheumatol* 2014;33:49–55.
10 Pouchot J, Sampalis JS, Beaudet F, *et al*. Adult still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991;70:118–36.
11 Ruscitti P, Cipriani P, Masedu F, *et al*. Adult-Onset still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. *BMC Med* 2016;14:194.
12 Rau M, Schiller M, Krienke S, *et al*. Clinical manifestations but not cytokine profiles differentiate adult-onset still's disease and sepsis. *J Rheumatol* 2010;37:2369–76.
13 Vastert SJ, Jamilloux Y, Quartier P, *et al*. Anakinra in children and adults with still's disease. *Rheumatology* 2019;58:vi9–22.
14 Feist E, Quartier P, Fautrel B, *et al*. Efficacy and safety of canakinumab in patients with still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. *Clin Exp Rheumatol* 2018;36:668–75.
15 Vastert SJ, de Jager W, Noordman BJ, *et al*. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. *Arthritis Rheumatol* 2014;66:1034–43.
16 Ter Haar NM, van Dijkhuizen EHP, Swart JF, *et al*. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. *Arthritis Rheumatol* 2019;71:1163–73.
17 Gabay C, Fautrel B, Rech J, *et al*. Open-Label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset still's disease. *Ann Rheum Dis* 2018;77:840–7.
18 Kaneko Y, Kameda H, Ikeda K, *et al*. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis* 2018;77:1720–9.
19 Thornton T. Clinical judgement, expertise and skilled coping. *J Eval Clin Pract* 2010;16:284–91.
20 Kienle GS, Kiene H. Clinical judgement and the medical profession. *J Eval Clin Pract* 2011;17:621–7.