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 Muraviov and Muraviova¹ 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, Muraviov and Muraviova 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 Muraviov and Muraviova,^{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, Muraviov and Muraviova 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 by¹ Muraviov and Muraviova 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.

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