Changing the outcome measures, changing the results? The urgent need of a specific disease activity score to adult-onset Still's disease

We read with great interest the article by Kedor *et al*[1] on the efficacy of canakinumab, an interleukin (IL)−1β antagonist, on patients with adult-onset Still's disease (AOSD). In this multicentre, double-blind, randomised, placebo-controlled trial, 36 patients with active joint involvement were enrolled[1]; this is the largest clinical trial performed on AOSD so far. Moreover, the results of this trial are of considerable interest in this field, considering the challenge of arranging prospective studies on a rare disease. Despite the improvement of many articular secondary measures, the primary outcome, the proportion of patients with a clinically relevant reduction of the articular manifestation measured by change in disease activity score (ΔDAS28(ESR) >1.2) at week 12, did not achieve statistical significance.[1] Apparently, this finding seems to be in contrast with the strong scientific rationale, which is behind the study, of inhibiting IL-1β in AOSD and with the confirmed efficacy of canakinumab reported in the juvenile counterpart of AOSD.[2 3] As previously performed,[4 5] the authors used the DAS28 to assess the disease activity, selecting patients with active joint involvement. Although of importance, the assessment of articular pattern could not entirely evaluate the clinical manifestations of AOSD, characterised by both systemic and articular features. In fact, during flares, patients are frequently affected by fever, which is the expression of systemic inflammation of the disease, associated with arthritis, either oligo-arthritis or bilateral symmetrical rheumatoid arthritis-like polyarthritis, with a usual migrating pattern.[3] On these bases, it must be pointed out that this clinical issue reflects a big unmet need in the management of AOSD due to the lack of standardised outcome measures. In fact, an international agreement is still missing concerning the assessment of disease activity, the definition of refractory patients and the evaluation of remission. To overcome these limits, EULAR is supporting a specific working group devoted to develop and validate a disease activity score in AOSD, "*Development and validation of a disease activity score in adult onset Still's Disease: the DAVID project* (CLI113)". The EULAR Task Force includes experts, selected according to their field of interest and knowledge on AOSD, from a variety of European countries who are working, by a synergistic effort, to develop recommendations/points to consider for a clinical tool measuring disease activity in AOSD and a definition of remission readily transferable into clinical practice.

Presently, the mechanism of action of some new drugs supports a strong rationale for using such therapies on AOSD.[6] However, the possibility to plan clinical trials is strongly limited by the lack of specifically validated outcome measures with the consequent usage of surrogate measures, derived from other diseases, which could possibly lead to false-negative results. Furthermore, a validated score measuring disease activity would also allow effective comparisons between studies, reducing the heterogeneity of the results. Such a score might also reduce healthcare costs due to decreasing a potentially unjustified use of expensive therapeutic strategies. Finally, this specifically designed disease activity score would allow to re-assess the data of previous clinical trials to fully evaluate the efficacy of study drugs on AOSD.

In conclusion, the clinical trial by Kedor *et al*[1] is a further example of how the absence of validated measures could impair the expected positive results, despite the strong scientific rationale. Thus, the lack of standardised outcome measures is an urgent need to improve the management of patients with AOSD. In fact, the validated disease activity score, which will be generated by the EULAR Task Force, will allow researchers, on the one hand, to better and comprehensively investigate disease activity in these patients and, on the other, a potentially new repurposing of drugs which apparently did not show their entire usefulness in AOSD.

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