Response to: 'MS score in systemic juvenile idiopathic arthritis: suitable for routine use?' by Chi *et al*

We thank Chi *et al*[1] for their interest in our diagnostic score for macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA).[2]

Chi *et al* argue that the collection of MAS patient data at the onset of the syndrome and of sJIA patient data not only at the onset of the illness but also during a flare could have caused a selection bias. However, the primary purpose of our analysis was to scrutinise the ability of clinical and laboratory features to discriminate between MAS and active sJIA without MAS. Because the main sJIA manifestations at disease onset or at the time of a flare with ongoing systemic features are clinically similar, we thought that both time points were equally suitable as controls. Note that only 22% of MAS episodes observed in our series developed at onset of sJIA, whereas all the other instances occurred at various times during the underlying disease course.[3]

Regarding central nervous system dysfunction, we included in the definition the neuropsychiatric symptoms that are traditionally described as part of this organ involvement in MAS.[4–6] We recognise, however, that the definitions of headache and mood changes were not sufficiently detailed. In our view, headache can be related to MAS when it is severe, unrelenting, unresponsive to analgesics and persistent independently of fever. Mood changes can be defined as sudden mood alteration or unexplained major depression.

Another concern raised by Chi *et al* is that the presence of fever as mandatory criterion may lead to missed or delayed diagnosis of MAS, as fever may be suppressed by treatment with corticosteroids or IL-1 inhibitors. The choice of placing fever as a prerequisite for the diagnosis of MAS was based on the notion that it was the mostly highly ranked clinical feature of MAS in a Delphi survey conducted among international paediatric rheumatologists[7] and was considered a fundamental requirement for the classification of MAS by the expert panel that devised the 2016 classification criteria for MAS complicating sJIA.[8] In addition, fever was reported in 96.1% of 362 patients with sJIA-associated MAS collected in a multinational multicentre survey,[3] which confirms its key relevance in the clinical picture of MAS. However, a recent systematic literature review has shown that the 2016 MAS classification criteria may miss some episodes of MAS occurring in patients with sJIA under treatment with IL-1 and IL-6 blocking agents, owing to the substantial alterations in MAS features induced by these biologics, including lack of fever.[9] Due to the small number of patients under biological treatments in our database, we could not test the MS score in a subgroup of patients who had MAS under therapy with IL-1 and IL-6 inhibitors. More data from the real world of clinical practice are needed to establish whether the score should be refined to increase its power to pick up the instances of MAS occurring during treatment with biological medications.

As a final note, Chi *et al* contend that the exclusion of soluble CD25 and natural killer cell activity may affect the sensitivity and specificity of MAS detection. Although we agree that these biomarkers are important indicators of increased T cell activation and impaired cytolytic function and may help to detect subclinical instances of the syndrome, they are not readily available in most paediatric rheumatology centres, particularly in resource-limited areas. Furthermore, because these tests take time to complete they may not be suited to diagnose MAS timely at patient bedside. Nevertheless, the role of suggested immunological parameters, together with that of sCD163 IL-18, CXCL9 and others, in the routine diagnosis of MAS is worth being investigated in the future.

In conclusion, we are grateful to Chi *et al* because their comments led us to clarify some aspects of the MAS/sJIA (MS) score that may enhance its applicability. Further insights into the validity of the score will be obtained through its widespread use in clinical practice.

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