

Response to: 'Time to personalise the treatment of anti-MDA-5 associated lung disease' by Lake *et al*

We have with interest read the comments raised by Lake *et al* in the e-letter titled 'Time to personalise the treatment of anti-MDA-5 associated lung disease' to be published in your journal.¹ We thank the authors for sharing their insights on the 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIM) and their major subgroups.² Lake and colleagues are concerned that these classification criteria are not including rare specific subsets such as dermatomyositis (DM) or amyopathic DM associated with antineoplastic differentiation-associated protein 5 (MDA5). They fear that this will in turn prevent clinicians and researchers from exploring new therapeutic approaches for this population frequently affected by rapidly progressive interstitial lung disease (RPILD), a complication associated with fatal outcomes.^{3,4} Dr Malaviya raised a similar concern when discussing the importance of myositis-specific autoantibodies (MSA) in classifying subgroups of IIM, exemplified by four subgroups of amyopathic DM associated with different MSA and with different clinical phenotypes and response to treatment, one being anti-MDA5 antibody positive amyopathic DM.⁵ We responded to Dr Malaviya's concern and addressed the ongoing international collaborative effort of systematic collection of autoantibody and clinical data for patients with IIM.⁶ In this letter, we would like to address the concern raised by Lake and colleagues. Classification criteria and their influence on population selection for clinical trials surely have an impact on formulating treatment guidelines in conditions such as idiopathic inflammatory myositis (IIM). Classification of a heterogeneous group of diseases with multiple possible organ involvement, considerable overlapping features and different underlying pathological molecular mechanisms is a challenge. The 2017 EULAR/ACR IIM classification criteria were developed using the expertise of rheumatologists, dermatologists, neurologists and paediatricians in an attempt to reflect as closely as possible the clinical spectrum of IIM. As those criteria are data-driven, certain clinical characteristics such as most of the MSA could not be included in the final variables given their rarity and the fact that some of these MSA were not widely available for clinical use at time of data collection. However, the inclusion of anti-histidyl-tRNA synthetase (Jo1) in the current version of the criteria is a step forward in incorporating MSA as important discriminating factors in IIM classification. By no means are we suggesting to clinicians or researchers that MSA status do not have a diagnostic and prognostic utility in practice. It seems appropriate to emphasise that classification criteria should not be used as diagnostic criteria and that clinicians should consider all available evidence pointing to an IIM diagnosis to tailor their management.⁷

As emphasised by Lake *et al*, ILD is a serious and possibly fatal extramuscular manifestation of IIM. We agree that revision of the EULAR/ACR criteria should address this concern, as ILD yielded a strong association with having IIM in the dataset used to develop the criteria.⁸ In a previous response letter, we have discussed the process leading up to the final criteria and the selection process involving ILD and other extramuscular manifestations.⁹ From our local experience with the Karolinska University Hospital IIM cohort, out of our

14 patients with a positive anti-MDA5 autoantibody, 13 (93%) are classifiable using the new classification criteria as either DM (n=9) or ADM (n=4). Only one patient is not classifiable as he was diagnosed while critically ill with RPILD in the intensive care unit and died shortly after diagnosis, not unlike the case described by Lake *et al*. In that regard, we believe that most IIM classification criteria are performing poorly in an acute setting such as described above, given the challenge of assessing for muscle involvement by manual testing or muscle biopsy. We believe that in the example presented by Lake *et al*, the question is not if the 2017 EULAR/ACR IIM classification criteria are capturing or not anti-MDA5 cases, as they do. The question is if the subset assigned is an adequate reflection of the clinical phenotype associated with the condition. We must agree with the authors of the letter that in the current version of the EULAR/ACR IIM classification criteria, it is not possible to identify subgroups of rare phenotypes subclassified by MSA status. Our hope is that with time, international collaboration and expanding data will permit inclusion of other MSA in a data-driven validated revision of the EULAR/ACR IIM classification criteria.

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