Editorial

Issues in the classification of myositis patients: an ongoing process

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In the last decades, our approach to myositis patients deeply changed, and we are expecting further changes even shortly. For several years, polymyositis and dermatomyositis were the only diseases included in the group of idiopathic inflammatory myopathies (IIMs), as the "1975 Bohan and Peter Criteria for polymyositis and dermatomyositis" clearly showed (1). These criteria led to an overdiagnosis of polymyositis, without allowing the differential diagnosis with conditions such as inclusion body myositis (IBM), hypothyroid myopathy, self-limited statin myopathy, and inherited myopathies, including dysferlinopathy, calpainopathy, and facioscapulohumeral dystrophy (2, 3). The identification of myositis-specific and associated autoantibodies was crucial for the evolution of our knowledge on myositis. Thanks to these antibodies, different new entities were defined and clinically characterised. In 1980, the anti-Jo1 was the first anti aminoacyl-tRNA synthetase (anti-ARS) antibody recognised (4). These antibodies target single-stranded, non-coding RNA molecules involved in the recognition and pairing of every specific amino acid to his cognate tRNA, playing a key role in protein synthesis (5). In 1995 Tanimoto *et al*. included the anti-Jo1 in their classification criteria for polymyositis and dermatomyositis (6), but since then, 9 more anti-ARS were identified, including the anti-PL7, anti-PL12, anti-OJ, anti-EJ, anti-KS, anti-Ha, anti-Zo (7), and the recently recognised anti-Ly and anti-valyl tRNA antibodies (8, 9). However, the number of anti-ARS may be much higher, because also the remaining 10 ARS can potentially be targeted by specific antibodies, as well as different components of the recently described three-dimensional structure of the multi-tRNA synthetase complex (10). This point is not secondary, because anti-ARS are considered the serological markers of the so-called antisynthetase syndrome (ASSD), a clinically established entity characterised by the classic triad of arthritis, myositis, and interstitial lung disease, and by a specific and peculiar clinical spectrum time course (11), which has led many experts to classify it separately from poly- and dermatomyositis (12, 13). Different definitions of ASSD have been proposed (14-16), or used in the daily clinical practice (17), in all cases including lung and joint involvement. Furthermore, an ACR/EULAR initiative aimed at the development and validation of the first classification criteria of ASSD is ongoing (CLASS project) (17).

Similarly to the Tanimoto criteria (6), anti-Jo1 antibodies have been included in the 2017 EULAR/ACR criteria of idiopathic inflammatory myopathies (18). These data-driven criteria are aimed at providing a score expressing the probability of being classified as IIM and allow sub-classification into PM, DM, clinically amyopathic DM (CADM), juvenile DM, IBM and immune-mediated necrotising myopathy (IMNM). However, they mainly focus on muscle and skin involvement, without considering other clinical involvements or their specific autoantibodies. These criteria have been widely applied and surely represent a relevant step forward, but several discussion points have been raised since their publication, starting from the differentiation with the ASSD (19).

In this issue, Saygin *et al*. (20) presented a scoping review focused at supporting the revision of the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups (18).

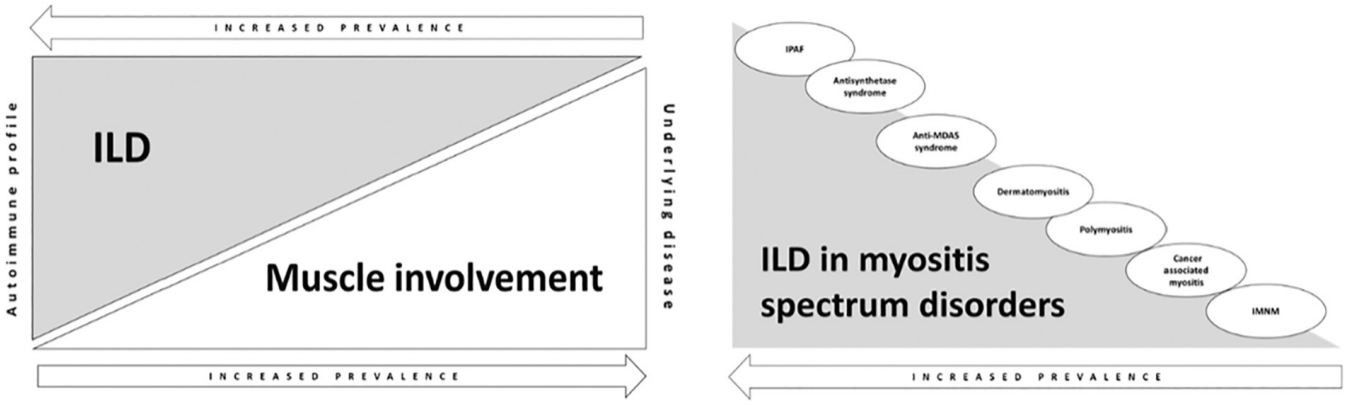

Fig. 1. The relationship between ILD and muscle involvement, according to the underlying disease and autoantibody profile.
ILD: interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features; IMNM: immune-mediated necrotising myopathie).

The authors identified different pitfalls in the criteria and suggested actions that a possible revision should take to overcome them. The focus is surely well directed, but we believe that some additional issues with these criteria need to be highlighted and hopefully addressed by the future revision.

We believe that more emphasis should be addressed toward those disease forms presenting without muscular involvement, especially ILD. These cases are not uncommon, considering that up to 20% of ASSD patients have no myositis (11), and myositis is not common even in both Asian (21) and not Asian (22) patients with anti-MDA5 syndrome. At present, these patients can be easily classified as interstitial pneumonia with autoimmune features (IPAF) (23), but not as IIMs (18), despite these conditions are commonly considered amongst the myositis spectrum disorder (MSD). Even the action proposed in the scoping review (20), namely the inclusion of ILD among the criteria, seem insufficient to address this issue, unless ILD (and not just skin involvement) is also to be considered as a condition potentially related to a clinically amyopathic form.

Furthermore, the current criteria (18) do not allow the classification of patients with short-term disease (<6 months). This feature can impact the planning of clinical trials addressed to anti-MDA5 positive patients with rapidly progressive (RP) ILD. In fact, RP-ILD is an early manifestation of the anti-MDA5 syndrome, mainly occurring in the first 2 months from disease onset (22). Considering that the main purpose of classification criteria is to plan clinical trials and that RP-ILD is one of the most critical feature of IIMs (12), the requirement of 6 months of disease duration before patients' categorisation, in our opinion needs to be deeply reconsidered in the future reviews.

Furthermore, the relationship between ILD and myositis spectrum disorder is surely relevant and related to the underlying subset definition strictly linked to the autoantibody profile, as highlighted in Figure 1.

Another relevant issue that was neglected by the scoping review is the inclusion of joint involvement in the criteria. Joint involvement is very common in patients with ASSD (11, 22, 24-26) and anti-MDA5 syndrome (22, 27), and arthritis may be the only presenting major feature of these diseases (24). Especially in the mainframe of ASSD, joint involvement is a pivotal feature, as evidenced by the fact that it is considered as an entry criterion in its currently available definitions (14-16).

Further efforts should be applied even in the definition of some clinical features and muscle enzymes testing. In our view, a more accurate definition of dysphagia is desirable, taking into account the different ways in which the condition may be diagnosed (patients-reported, EMG, barium swallowing test, FEES, etc.). A clear statement for the assessment of dysphagia should be warranted to clinicians. Moreover, the exclusion of aldolase from the muscle enzymes to be assessed also needs to be amended. In fact, it has been recently reported that isolated aldolase elevation can be found in many IIMs. Moreover, patients with DM and isolated aldolase elevation seem to display some peculiar features compared to DM patients with hyperCKemia (28).

One of the most important issues addressed by the scoping review is the one related to the inclusion of other MSAs, such as anti-NXP2, anti-SRP, anti-HMGCR, anti-Mi2, or anti-SAE (13) in the revised classification criteria. Although we agree with the authors on the fundamental importance of these antibodies in the classification of myositis, we would also like to emphasise that this risks becoming a "never ending story", since new antibodies will be detected, year after year. We believe that the new criteria should provide for a periodic update of the antibodies to be included in the classification. On this purpose, we would also recommend the authors to consider the inclusion of anti-Ro52 in the revised criteria, given how commonly it can be detected in ASSD (11, 29), anti-MDA5 syndrome (22), and DM (30), in all cases with a strict connection with ILD and RP-ILD occurrence.

Finally, the authors stated that these classification criteria also aim at subclassifying different subsets of MSD. This is, in our opinion, the most relevant discussion point, that fundamentally questions the wisdom of these criteria and raises the most burning questions. Are we willing to include under the same umbrella such different conditions, with different manifestations, clinical spectrum time courses (11, 22,

31), cancer risk (32), and even with different potential triggers and pathogenesis mechanisms (33-35)? Will a single set of criteria really allow the correct classification and thus the drafting of adequate clinical trials on such diverse conditions that often, as we learned from the clinical experience, require different treatments? A parallelism with the setting of arthritis might help us finding the answers to these questions. In fact, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis although targeting joints, are separate clinical entities, for which specific clinical trials are conducted and, therefore, different treatments are recommended. In this perspect, we agree with Saygin *et al*. (20) when they state that ASSD can be considered as a distinct subtype of MSD, and therefore we ask ourselves whether it is not appropriate to exclude anti-ARS from the criteria for IIMs. And again, given that a specific set of criteria for ASSD is being drafted, demonstrating that it now being recognised as a clinical entity on its own, we wonder whether the time has come for other condition, such as scleromyositis (36, 37), to follow the same path.

Taking together all the comments and the review, it is evident that myositis criteria should be reassessed and reconsidered. We should improve our approach and we should work in a multidisciplinary manner, changing the usual perspectives we applied until a few years ago to myositis patients. In our daily practice, one of the starting points should be the pneumo-rheumatology outpatient clinics, which may improve our approach to connective tissue diseases related ILD in general and to MSD in particular (38-40). To some extent, even the terms IIMs and MSD could be considered limiting, given the knowledge we now have about the wide spectrum of manifestations of these diseases, where the muscle is not always the main character (41).

A large discussion will arise in the future, and with this yearly monographic issue on myositis we are ready to support the different souls of the myositis universe, considering that, as stated (42) for ASSD, even myositis is not just an inflammatory myopathy.

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