Editorial

The myositis landscape in clinical trials: 2025 and beyond

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In recent years the number of clinical trials addressing myositis has steadily increased. Today many trials, not only limited to muscle involvement, are ongoing or planned, including among others the one described in this issue (1, 2). This trend aligns with the growing attention of various stakeholders, such as pharmaceutical companies, scientific societies, regulatory agencies, and National and International Government Organisations, on rare conditions in general and on myositis in particular (3-5). This interest led to several advances in the setting of myositis, including the publication of the 2017 ACR/EULAR criteria for idiopathic inflammatory myopathies (6), the 2016 ACR/EULAR response criteria, and inspired the creation of this monothematic annual issue as the official organ of the International Myositis Society (iMyos) (7). Furthermore, the myositis community also defined the clinical spectrum time course of the antisynthetase (ASSD) (8) and of the anti-MDA5 (9) syndromes, and started the CLASS project, to define the first validated Classification criteria of ASSD (10), where joint and lung involvement will have a key role in the Classification process. Moreover, in 2017 the European Commission launched the European Reference Networks (ERNs), cross-border networks for highly specialised healthcare of rare and complex diseases including inflammatory myopathies.

Being the approach to myositis multidisciplinary (11), myositis refers to different ERNs, such as ReCONNET, involving rheumatologists, Euro-NMD involving neuromuscular specialists, and LUNG, involving pulmonologists, in all cases with established collaborations. A fundamental feature of this program is that the participating centres must be officially endorsed by their national health authorities and regularly monitored for their efficiency by the European Commission (12).

At the same time, EMA and other agencies have developed precise recommendations on how to design and conduct clinical trials in small populations and rare diseases (13-15). For instance, the application of these suggestions has recently inspired a successful clinical trial in Behçet's disease (16).

In this issue, Bishnoi *et al*. (17) introduces the Myositis Clinical Trials Consortium (MCTC), an international initiative designed to increase the number of centres participating in myositis trials. This project parallels a similar network, the Myositis International Health and Research Collaborative Alliance (MIHRA) (18).

Bishnoi *et al*. have clearly explained the aim of their initiative and its added value, together with the groundwork necessary for its success. In this respect, however, a number of critical points should be highlighted: the most important are the significant differences in clinical practices, laboratory protocols, follow-up strategies, cultural gaps and ground-therapies driven by the expertise of the centres involved and variability of national healthcare systems.

This heterogeneity represents a significant obstacle to increasing the number of centres equipped to participate in myositis trials (19). Addressing this variability is essential to expanding trial participation while ensuring high standards of care.

Furthermore, given the rarity of these diseases, in order to avoid inclusion biases the single centres should limit their participation in concomitant competing trials.

Finally, other issues are directly related to clinical trials. The first issue concerns project design, including chal-

lenges with inclusion/exclusion criteria, identifying primary and secondary endpoints, selecting outcome measures, and designing interventional trials. For a clinical trial on myositis, we need different outcome measures and an extended effort from the different actors on the scene. Although patients' reported outcomes may be useful, they can represent only a minimal part of the solution.

The second one is that clinical trials on myositis are complex, frequently requiring several visits with complete physical examination and analysis, together with the complete knowledge of different outcome measures applied. Only centres with all the necessary facilities and skills can be included.

Taken together, there is no doubt that these international initiatives (17, 18) are potentially invaluable contributions to fostering the knowledge and management of complex and overlooked multidisciplinary diseases such as myositis, providing that they become inclusive of the most important competent centres worldwide. The success of a similar international project in paediatric rheumatology, PRINTO (20, 21) may inspire the future progress of their work.

Now that we have the actors, let us start to produce the movie.

References

1. NEEDHAM M, DIMACHKIE MM, BEER K *et al*.: Challenges in international investigator-led rare disease clinical trial and the case of optimism in inclusion body myositis: a Neuromuscular Study Group. *Clin Exp Rheumatol* 2025; 43(2): 309-15. https://doi.org/10.55563/clinexprheumatol/dyjcsn
2. BADRISING U, HENDERSON R, REDDEL S *et al*.: Optimism in IBM: a double-blind randomised controlled phase III trial investigating the effect of sirolimus on disease progression in patients with inclusion body myositis as measured by the IBM Functional Rating Scale. *Clin Exp Rheumatol* 2025; 43(2): 316-25. https://doi.org/10.55563/clinexprheumatol/zvffa0
3. MEYER A, SCIRÈ CA, TALARICO R *et al*.: Idiopathic inflammatory myopathies: narrative review of unmet needs in clinical practice guidelines. *RMD Open* 2018; 4 (Suppl 1): e000784. https://doi.org/10.1136/rmdopen-2018-000784
4. TALARICO R, AGUILERA S, ALEXANDER T *et al*.: The added value of a European Reference Network on rare and complex connective tissue and musculoskeletal diseases: insights after the first 5 years of the ERN ReCONNET. *Clin Exp Rheumatol* 2022; 40 (Suppl. 134): S3-11. https://doi.org/10.55563/clinexprheumatol/d2qz38
5. ZANFRAMUNDO G, SELVA-O'CALLAGHAN A, GONZÁLEZ-GAY MÁ, MONTECUCCO C, CAVAGNA L: Issues in the classification of myositis patients: an ongoing process. *Clin Exp Rheumatol* 2024; 42(2): 225-28. https://doi.org/10.55563/clinexprheumatol/8u8p8x
6. LUNDBERG IE, TJÄRNLUND A, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. *Arthritis Rheumatol* 2017; 69(12): 2271-82. https://doi.org/10.1002/art.40320
7. AGGARWAL R, RIDER LG, RUPERTO N *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Adult Dermatomyositis and Polymyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Arthritis Rheumatol* 2017; 69(5): 898-910. https://doi.org/10.1002/art.40064
8. CAVAGNA L, TRALLERO-ARAGUÁS E, MELONI F *et al*.: Influence of antisynthetase antibodies specificities on antisynthetase syndrome clinical spectrum time course. *J Clin Med* 2019; 8(11): 2013. https://doi.org/10.3390/jcm8112013
9. CAVAGNA L, MELONI F, MEYER A *et al*.: Clinical spectrum time course in non-Asian patients positive for anti-MDA5 antibodies. *Clin Exp Rheumatol* 2022; 40(2): 274-83. https://doi.org/10.55563/clinexprheumatol/di1083
10. ZANFRAMUNDO G, FAGHIHI-KASHANI S, SCIRÈ CA *et al*.: Defining anti-synthetase syndrome: a systematic literature review. *Clin Exp Rheumatol* 2022; 40(2): 309-19. https://doi.org/10.55563/clinexprheumatol/8xj0b9
11. CHARTRAND S, SWIGRIS JJ, PEYKOVA L, CHUNG J, FISCHER A: A multidisciplinary evaluation helps identify the antisynthetase syndrome in patients presenting as idiopathic interstitial pneumonia. *J Rheumatol* 2016; 43(5): 887-92. https://doi.org/10.3899/jrheum.150966
12. EUROPEAN COMMISSION: Directorate-General for Health and Food Safety. European Reference Networks - Working for patients with rare, low-prevalence and complex diseases - Share, care, cure. Publications Office of the European Union, 2023. https://data.europa.eu/doi/10.2875/701174
13. DAY S, JONKER AH, LAU LPL *et al*.: Recommendations for the design of small population clinical trials. *Orphanet J Rare Dis* 2018; 13(1): 195. https://doi.org/10.1186/s13023-018-0931-2
14. GAMERMAN V, CAI T, ELSÄßER A: Pragmatic randomized clinical trials: best practices and statistical guidance. *Health Serv Outcomes Res Method* 2019; 19(1): 23-35. https://doi.org/10.1007/s10742-018-0192-5
15. MISHRA S, VENKATESH MP: Rare disease clinical trials in the European Union: navigating regulatory and clinical challenges. *Orphanet J Rare Dis* 2024; 19(1): 285. https://doi.org/10.1186/s13023-024-03146-5
16. TALARICO R, ITALIANO N, EMMI G *et al*.: Efficacy and safety of infliximab or adalimumab in severe mucocutaneous Behçet's syndrome refractory to traditional immunosuppressants: a 6-month, multicentre, randomised controlled, prospective, parallel group, single-blind trial. *Ann Rheum Dis* 2024 Oct 17. https://doi.org/10.1136/ard-2024-226113
17. BISHNOI A, TANG IYK, YOSHIDA A *et al*.: The Myositis Clinical Trials Consortium (MCTC): an international collaborative initiative to promote clinical trials in adult and juvenile myositis. *Clin Exp Rheumatol* 2025; 43(2): 202-10. https://doi.org/10.55563/clinexprheumatol/k7665a
18. SAKETKOO LA, PAIK JJ, ALEXANDERSON H *et al*.: Collaborative research in myositis-related disorders: MIHRA, a global shared community model. *Clin Exp Rheumatol* 2024; 42(2): 207-12. https://doi.org/10.55563/clinexprheumatol/hc1lsf
19. ZIADE N, AOUDE M, HMAMOUCHI I *et al*.: Global disparities in the treatment of idiopathic inflammatory myopathies: results from an international online survey study. *Rheumatology* 2024; 63(3): 657-64. https://doi.org/10.1093/rheumatology/kead250
20. RUPERTO N, MARTINI A: Network in pediatric rheumatology: the example of the Pediatric Rheumatology International Trials Organization. *World J Pediatr* 2008; 4(3): 186-91. https://doi.org/10.1007/s12519-008-0034-6
21. MARTINI A: Juvenile idiopathic arthritis in the world. *J Environ Rheumatol* 2024; 1(1): 23-30. https://doi.org/10.55563/jer/axe7tr