# Current myositis clinical trials and tribulations

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## ABSTRACT

With improved understanding of disease pathogenesis and availability of outcome measures, there has been a remarkable increase in the number of therapeutic clinical trials in idiopathic inflammatory myopathies (myositis) over the last three years reaching as many as five trials per site. These trials share similar design and inclusion/exclusion criteria resulting in a competitive clinical trial landscape in myositis. While these are exciting times for the myositis field, we have a number of concerns about the design and conduct of the myositis trials. These include competitive landscape, lengthy placebo arms, underrepresentation of minority groups among participants, use of patient reported outcome measures with limited/no data on validity in myositis, antiquated disease classification criteria, and unclear performance of the ACR/EULAR Myositis Response Criteria in skin-predominant patients despite inclusion of these patients in trials. In this viewpoint, we further discuss these concerns and offer potential solutions such as including patient perspectives in the trial design and adoption of innovative frameworks.

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous autoimmune diseases including dermatomyositis, polymyositis, anti-synthetase syndrome, immune-mediated necrotising myopathy and inclusion body myositis (IBM). There are currently three therapies approved by the US Food and Drug Administration (FDA), while intravenous immunoglobulin is the only one approved based on a placebo controlled randomised trial.[1 2] With improved understanding of the disease pathogenesis and availability of outcome measures with adequate measurement properties, there has been a dramatic increase in the number of myositis therapeutic clinical trials over the last 3 years (table 1). While an expanding list of potential therapeutic options with various different mechanisms of action for patients with myositis represents a time of excitement and hope, this enthusiasm should be tempered given several concerns with regard to the conduct of current myositis clinical trials.

## A COMPETITIVE CLINICAL TRIALS LANDSCAPE IN A RARE DISEASE

There are currently as many as five simultaneous active myositis therapeutic trials with similar inclusion/exclusion criteria being conducted at several participating sites resulting in a competitive clinical trial landscape in myositis which raises concerns for recruitment. To our knowledge, this is the largest number of industry-sponsored myositis clinical trials to date that are recruiting simultaneously with a total recruitment goal of 1427 patients (table 1). Although inability to reach recruitment goals may lower the enthusiasm to conduct trials in this rare disease, these trials are conducted simultaneously at numerous centres across the world with the goal of improving recruitment rates. To better address this, different trial designs should strongly be considered: (1) adaptive clinical trial designs in which the number of participants is continually refined based on interim data results and (2) platform trials that test multiple drugs in parallel under a single protocol. Harmonising the regulatory requirements of concurrent trials under a single infrastructure and using a shared, common placebo arm with these innovative trial designs could significantly decrease the patient burden, increase participation, reduce the cost and administrative burden on the investigators and coordinators, and ultimately expedite drug discovery in IIM. In fact, platform trials have been highly successful in other rare diseases such as amyotrophic lateral sclerosis (ALS) and could be particularly relevant to myositis given that the inclusion/exclusion criteria, endpoints and design across the current trials are similar.[3] Further, in our experience, one of the major patient-reported barriers to trial participation is potential assignment to the placebo arm. This concern is magnified in instances when the placebo arm is mandated to be lengthy by the FDA due to perceived safety concerns with novel agents. Platform trials with several arms and open-label extensions after study completion increase the chance of patients to receive novel therapies. Specifically, when a phase III trial is pursued following a phase II trial, it would be helpful to have the option to continue the study drug until the phase III trial is completed if the study drug has benefited the patient. Despite these benefits, platform trials are not attractive to stakeholders due to operational complexities and their high cost requiring an integrated funding model with multiple partners.[4] However, these challenges can be overcome through independent organisations that can coordinate buy-in and engagement between multiple stakeholders and provide a centralised governance structure (such as the new organization named Myositis International Health and Research Collaborative Alliance [MIHRA]). Strong research networks and active patient advocacy organisations facilitated the successful implementation of the platform trials in ALS which can be emulated in myositis.[3]

## DIVERSITY, EQUITY AND INCLUSION RECRUITMENT BARRIERS AND THE USE OF DECENTRALISED TRIAL DESIGNS

Black people and Hispanics/Latinos traditionally constitute <5% of participants in myositis therapeutic trials despite the reported more severe

**Table 1** Industry sponsored, active, multicenter myositis clinical trials (excluding inclusion body myositis) that are recruiting adult participants (obtained from ClinicalTrials.gov)

| Study drug (route) | Key inclusion criteria | Primary endpoint(s) | Estimated enrolment target | Design | Treatment duration |
|---|---|---|---|---|---|
| Brepocitinib (PO) | Active muscle AND skin disease (DM) | Total improvement score | 225 | Phase III, double-blind, placebo controlled RCT | 52 weeks |
| Efgartigimod PH20 (SC) | Active muscle disease (DM, JDM, PM, IMNM) | Total improvement score | 240 | Phase II/III, double-blind, placebo controlled RCT | Phase II: 24 weeks Phase III: 52 weeks |
| Enpatoran (PO) | Active muscle disease (DM, PM) | Total improvement score, adverse events, change in vitals | 40 | Phase IIa, double-blind, placebo controlled RCT | 24 weeks |
| GLPG3667 (PO) | Active muscle disease (DM) | Percentage of patients with at least minimal improvement in Myositis Response Criteria | 62 | Phase II, double-blind, placebo controlled RCT | 24 weeks |
| Immunoglobulin Pro20 (SC) | Active muscle disease OR rash (DM) | Responder rate (at least minimal improvement in Myositis Response Criteria) | 126 | Phase III, double-blind, placebo controlled RCT | 24 weeks |
| Nipocalimab (IV) | Active DM, IMNM, ASyS | Percentage of patients with at least minimal improvement in Myositis Response Criteria and prednisone ≤5 mg/daily | 200 | Phase II, double-blind, placebo controlled RCT | 52 weeks |
| Ravulizumab (IV) | Active DM | Percentage of patients with at least moderate improvement in Myositis Response Criteria | 150 | Phase II/III, double-blind, placebo controlled RCT | 50 weeks |
| PF-06823859 (anti-interferon beta therapy; IV) | Active DM or PM | At least moderate improvement in Myositis Response Criteria | 270 | Phase III, placebo controlled RCT | 52 weeks |
| Daxdilimab (SC) | Active muscle disease (DM, ASyS) | Total improvement score | 96 | Phase II, placebo controlled RCT | 44 weeks |
| Autologous CD19-specific Chimeric Antigen Receptor T Cells (CABA-201; IV) | Active muscle disease (DM, ASyS, IMNM) | Adverse events | 18 | Phase I/II, open label single arm trial | Single infusion |

ASyS, anti-synthetase syndrome; DM, dermatomyositis; IMNM, immune-mediated necrotising myopathy; IV, intravenous; JDM, juvenile dermatomyositis; PM, polymyositis; PO, per oral; RCT, randomised controlled trial; SC, subcutaneous.

disease course and differences in clinical manifestations in these patients.[1 5–7] The limited diversity in myositis clinical trials could result from several barriers including trial availability as well as access and enrolment practices requiring participants from underserved communities to travel to large academic centres for clinical trials which may not be plausible due to costs, time constraints and functional disability observed in approximately one in four patients with IIM.[8] Trial participation requires significant time commitment and financial resources due to missed workday and out-of-pocket costs related to travel. Direct and indirect costs of participation and transportation are among the most commonly reported barriers to clinical trial participation among under-represented minorities.[9] Therefore, appropriate compensation of participants needs to be carefully addressed by the investigators and the FDA.

Enhancing diversity in trials could also be achieved by adopting fully or hybrid decentralised clinical trials (DCTs). DCTs involve using digital health technologies to conduct telehealth visits at patients' homes or local healthcare facilities. By eliminating the need for travel and reducing patient costs, DCTs hold immense potential to meet recruitment goals and to facilitate participation of individuals with disabilities, older adults and minority groups from underserved areas in trials. However, these trials often require additional training of the study personnel, several contracted services and careful coordination of activities by the local sites. Thus, participating sites should be appropriately compensated to support the new infrastructure required for these trials. Recognising the value in DCTs, the FDA also recently published a draft guidance document.[10] While this is an excellent first step, there are potential obstacles. Sponsors are required to adhere to all pertinent local laws, regulations and licensing requirements related to medical practice, drug supply chain and dispensing and intellectual property administration when executing a DCT. This may require navigating complex and changeable laws across multiple US states. However, these challenges can be mitigated by early engagement with the regulatory bodies during trial design.[11] In fact, a recent myositis-associated interstitial lung disease trial (NCT05335278) adopts DCT design which will provide an opportunity to examine the feasibility of such trials in IIM.

## PATIENT-REPORTED OUTCOMES AND PATIENT-CENTRIC RESEARCH CHALLENGES

Design of diverse, patient-centric trials not only requires tackling barriers for enrolment but also incorporating reliable and valid patient-reported outcome measures assessing symptoms that matter most to patients with IIM and are available and validated in multiple languages. Despite the extensive body of work on patient-reported outcome measures, some trials use measures that have not been adequately studied in IIM. A decade of work of the Outcome Measures in Rheumatology (OMERACT) Myositis Working Group with patient focus groups in the USA, South Korea, the Netherlands and Sweden demonstrated these symptoms as physical function, pain interference and fatigue[12–14] and determined the instruments as PROMIS Physical Function (8b), Pain Interference (6a) and Fatigue (7a) to best capture these symptoms.[15] The evidence towards reliability, validity and responsiveness of these patient-reported outcome measures has been demonstrated in a large international cohort of patients from Australia, the Netherlands, Sweden, South Korea and the USA (in English, Dutch, Swedish and Korean) supporting their use as clinically meaningful patient-reported outcome measures in myositis trials recruiting participants from across the world.[16] For patients with skin-predominant disease, additional validated skin-directed quality of life measures should also be considered.[17]

## ANTIQUATED CLASSIFICATION CRITERIA

In 2017, the European Alliance of Associations for Rheumatology and American College of Rheumatology (EULAR/ACR) Classification Criteria for adult and juvenile IIM were developed with a data-driven approach classifying the IIM subgroups of dermatomyositis, amyopathic dermatomyositis, IBM, polymyositis and juvenile dermatomyositis.[18] With the discovery of new autoantibodies in IIM associated with distinct clinicopathological phenotypes over the years, new IIM subtypes emerged including immune-mediated necrotising myopathy and anti-synthetase syndrome, and polymyositis is now recognised to constitute only a minority of the patients with IIM.[19] However, some trials continue to enrol patients with polymyositis which raises concern for generalisability of these results in real-world clinical practice. Further, lack of recognition of newer IIM subtypes hampers the ability to accurately classify these patients in the clinical trials. Revision of the current EULAR/ACR Myositis Classification Criteria can help better define newly recognised IIM subtypes for inclusion in the clinical trials and is currently underway.

## HETEROGENEITY OF DISEASE PRESENTATION AND EXPRESSION INCLUDING SKIN-DOMINANT DISEASE

The ACR/EULAR Myositis Response Criteria is a composite measure that is commonly used as primary endpoint in myositis clinical trials and reflects changes in six myositis core set measures.[20] These core set measures are Patient and Physician Reported Global Disease Activity, Health Assessment Questionnaire Disability Index, Extramuscular Global Disease Activity, manual muscle testing and muscle enzymes. Even though the majority of myositis clinical trials only enrol patients with active muscle disease, some trials allow for recruitment of patients with amyopathic/hypomyopathic disease as well. Prior studies suggest that the ACR/EULAR Myositis Response Criteria may not perform as well in patients with skin-predominant disease.[21 22] Therefore, further studies are required to understand the performance of the criteria in patients with skin-predominant disease.

In a relatively rare disease, it is also important to have a sensitive validated tool that captures meaningful change in skin disease from a patient perspective. The investigator global assessment (IGA) is often the preferred outcome measure by the regulatory agencies to assess improvement in skin disease. However, despite the validation and extensive use of IGA in psoriasis, it was only recently developed for dermatomyositis and failed to consistently discriminate between no and slight levels of improvement in a dermatomyositis clinical trial.[22] On the other hand, the Cutaneous Dermatomyositis Disease Area and Severity Index is a dermatomyositis-specific validated outcome measure and demonstrated a better sensitivity to change than IGA.[22–24] Acceptance of this measure by regulatory agencies would allow studies that target a large group of patients with amyopathic disease, expanding the therapeutic options for these severely impacted patients.

In summary, the competitive nature of the current myositis clinical trial landscape necessitates a more efficient and patient-focused approach. This can be achieved by (1) including patient perspectives in the trial design and execution, (2) using reliable and valid patient-reported outcome measures, (3) using enrichment strategies to actively promote diversity in recruitment, and (4) employing innovative trial frameworks like adaptive trial designs and DCTs when suitable. For optimal design of myositis clinical trials, it will be important to revise the EULAR/ACR Myositis Classification Criteria to include newer IIM subtypes, as well as to evaluate the performance of the ACR/EULAR Myositis Response Criteria in patients with predominantly skin-related disease.

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