Update on outcome assessment in myositis

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Abstract

The adult and juvenile idiopathic inflammatory myopathies (IIM) are systemic autoimmune diseases with the hallmark of muscle weakness and inflammation. We review the major tools available to clinicians and researchers to evaluate the outcome of myositis treatment. Validated, well-standardized measures to assess disease activity, known as core set measures, were developed by international myositis networks for use in clinical trials. Composite response criteria using weighted changes in the disease activity core set measures were developed and validated for adult and juvenile dermatomyositis and adult polymyositis, with different thresholds for minimal, moderate, and major improvement in adults and juveniles. Additional measures of muscle strength and function are being validated to improve content validity and sensitivity to change. A health-related quality-of-life measure with patient input in content is being developed for adult myositis patients. Disease state criteria, including criteria for inactive disease and remission, are being used as secondary trial endpoints. Muscle magnetic resonance imaging and immunologic biomarkers are promising to discriminate between disease activity and damage and may provide much-needed objective outcomes. These advances in the outcome assessment of myositis, along with

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collaborations among international networks, should facilitate further development of new therapies for myositis patients.

The idiopathic inflammatory myopathies (IIM) are a diverse group of autoimmune diseases characterized by chronic muscle inflammation and associated weakness. However, the IIM are complex, systemic diseases, with skeletal muscle involvement and frequent manifestations in other organ systems, including skin, joints, cardiopulmonary, gastrointestinal, and constitutional systems. Myositis researchers have come to understand that to adequately evaluate patients, assess their responses to therapies, and track long-term outcomes, it is necessary to assess the following constructs: disease activity, that is, the type, extent, and severity of reversible manifestations due to myositis; disease damage, which includes persistent changes from previously active disease related to scarring, atrophy, or fibrosis, long-term complications of therapy, or comorbid conditions; and patient-reported outcome measures (PROMs), including patient reports about physical function and health-related quality of life (HRQoL); as well as objective measures, such as imaging and biomarkers[1]. The formation of international collaborative groups of clinicians and researchers with special interest in myositis, including the International Myositis Assessment and Clinical Studies Group (IMACS) and the Paediatric Rheumatology International Trials Organisation (PRINTO)[2], has resulted in the development of standardized, well-validated assessment measures to evaluate these constructs. This review highlights recent developments in the assessment of myositis outcomes.

Core set measures

To assess patients with dermatomyositis (DM), polymyositis (PM), and juvenile dermatomyositis (JDM), international consortia of collaborating myositis investigators have developed and validated core set measures (CSMs) to assess disease activity in adult (IMACS) and juvenile patients (IMACS and PRINTO), as a minimum set of measures to comprehensively assess disease that would be performed and reported in all clinical studies and therapeutic trials of myositis (Table 1)[3]. These measures are practical, well-standardized, and reliable; they are easy to use in multicentre international studies, applicable to all forms of myositis, and are well validated. The PRINTO CSMs of activity for JDM received provisional acceptance by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)[3,4]. The IMACS CSMs have been recommended for use in patients with inclusion body myositis (IBM) without supporting validation studies, but they are not universally accepted for this subgroup[5].

The CSMs of disease activity have also been responsive to changes in disease activity, as demonstrated in several recent therapeutic trials for JDM and adult DM/PM[6–10]. The degree of change in each disease activity measure that is clinically significant has also been established, with at least 20% improvement in all IMACS or PRINTO CSMs, except 30% improvement in muscle enzymes, considered as a minimally clinically meaningful degree of change; moderate and major changes in CSMs of activity have also been defined[11]. The relative degree of importance of each measure has been determined using conjoint analysis, with muscle strength being considered most important and physician global activity (PGA)

followed by extramuscular activity as next in importance among the CSMs of disease activity for adult DM/PM and JDM[11].

The Myositis Damage Index, one of the primary CSMs for damage, has been validated for adult DM and PM and for JDM and used in several studies to assess long-term outcomes and disease sequelae (reviewed in[3]). Other measures of damage include physician global damage on a 10-cm Likert scale, as well as physical functional disability measures (Table 1). In addition, a measure of strength, as well as effects on growth and development, are also recommended by PRINTO in the assessment of damage in patients with JDM[4].

The CSMs of disease activity and damage have been widely adopted, not only by IMACS and PRINTO, but also by other groups[12,13]. Limitations in the CSMs include their lack of validation in IBM and variations among specialists in the assessment of strength and function, as detailed below.

Myositis response criteria

Response criteria provide standardized measurements of change in disease activity in response to a therapeutic intervention, as well as determination of whether a therapy is efficacious[14]. Initial partially validated response criteria for JDM, DM, and PM included the preliminary definitions of improvement, which required at least 20% improvement in a minimum of three of six CSMs of disease activity to determine that patients met minimal clinical improvement criteria[15,16]. These preliminary response criteria were used successfully as primary endpoints in several therapeutic trials, but they defined only minimal clinical improvement, were partially validated, and lacked good sensitivity and discriminatory validity in randomized trials[6–10].

The recent development of data- and consensus-driven conjoint analysis–based hybrid myositis response criteria for adult DM and PM and JDM, with quantitative assessment of improvement on a continuous scale and with different thresholds for minimal, moderate, and major improvement, marks a major advancement for assessing response to treatment in myositis clinical trials and studies[11]. These composite response criteria are based on weighted scores given to absolute percentage improvement in the six CSMs (Table 2). They were developed using large patient datasets; novel conjoint analysis methodology[17–21]; clinical trial validation; and, finally, consensus among adult and pediatric myositis experts who specialize in rheumatology, neurology, and dermatology. They are now approved as final myositis response criteria by the ACR and EULAR[22–25]. These criteria are the same for adult and juvenile patients, but with different thresholds for the varying degrees of response.

The 2016 ACR-EULAR myositis response criteria for adult PM/DM and JDM are hybrid criteria; that is, the same criteria can be used as a continuous or as a categorical outcome. These criteria generate a Total Improvement Score (TIS), on a scale of 0–100, which provides a quantitative degree of improvement for each subject that can be compared between treatment arms using mean or median scores of all enrolled patients. The TIS is the sum of the improvement reflected in each of the six CSMs of disease activity, but the individual CSMs are weighted, such that those deemed more important provide a greater

contribution to the final score. For example, changes in the manual muscle testing (MMT) and PGA scores are weighted more heavily than changes in the Health Assessment Questionnaire (HAQ) or most abnormal enzyme. Continuous measures may allow for better power (especially useful for pilot studies) and have greater sensitivity to change[26]. The criteria also provide categorical outcomes of minimal, moderate, and major improvement, where the proportion of patients achieving a desired response could be compared between treatment arms. These new response criteria also have several limitations; most notably, they cannot be used for disease flare or remission states (Box 1).

Measures of strength and function

The primary feature of the IIM is muscle weakness, for which the location, severity, and progression vary according to the phenotype and the patient[27–31]. Muscle weakness results in functional limitations (disability), which can be assessed by standardized motor tasks or estimated by questionnaires and scales. While muscle strength and functional measures are part of the CSMs, additional measures of strength and function have been examined, with the goals of improving performance and measurement sensitivity, covering aspects of disease not adequately assessed by CSMs, and developing more appropriate measures applicable to patients with IBM. The assessment of muscle strength and function requires adequate assessor training and patient participation for optimal performance. The choice of assessment tool should be based on the study population and goals of the study or clinical trial.

Muscle strength assessment

Muscle strength can be measured by several techniques (Table 3), generally in isometric conditions. MMT is used most commonly in clinic; has been validated for DM, PM, and JDM[3,27]; is a CSM[1,4]; and has been used as a primary or secondary outcome measure in many IIM therapeutic trials[1,6–11]. MMT has high practicality and low time and equipment requirements, as well as adequate inter- and intra-rater reliability and validity when performed by a trained examiner[32]. The limitations of MMT include poor sensitivity to change as well as floor and ceiling effects in natural history studies[3,27,33], but MMT has demonstrated good sensitivity to change in some clinical trials and has performed better than in natural history studies[1,6–8,10]. Moreover, strength assessed by MMT appears to improve to a smaller degree than other CSM in patients who are improving[11]. However, in two small therapeutic trials for DM and PM, MMT and fixed dynamometry (measured by maximal voluntary isometric contraction testing) had similar responsiveness to change[8,34]. Another advantage of MMT is that scores from different muscle groups can be aggregated to generate composite scores that can be used to gauge overall improvement or progression both in clinical practice and in clinical trials, which is not possible using absolute values of strength, as measured by dynamometers.

Muscle strength is increasingly being evaluated using dynamometer-based methods, which are used primarily in IBM and other neuromuscular diseases and rarely in PM or DM[28,29]. The clinometric properties of the measures depend on the metrological features of the dynamometer itself and on the operating procedures utilized. One of the advantages of

dynamometry is that it is more objective and less examiner-dependent than MMT. Combining the strength of different muscle groups is not consistent, however, due to their diversity in range. To compute composite values, it is necessary to express the data as a percentage of predictive values for age, weight, height, and/or sex. Normative data exist for several functions and for most of the methods, as well as for children, adolescents, and adults (Table 3). Dynamometry, to a lesser extent than MMT, may also have floor and ceiling effects, depending on the technique[29]. In IBM trials, hand-held dynamometry and maximal voluntary isometric contraction testing (mostly using hand-held or isokinetic dynamometers) have been used frequently, but different measures of strength are preferred by rheumatologists and neurologists. Quantitative muscle testing of quadriceps muscle using dynamometry appears to be most relevant as the affected muscle group that correlates best with disease progression and functional decline, and was more sensitive to change than the change in MMT in a natural history study of IBM[5,28,29,35].

Functional or disability measures

Physical impairments affect patients' day-to-day functioning, which can be assessed with task-oriented tests or functional assessment questionnaires (Table 4 and Supplementary Table 1). The generation of strength leads to the generation of movements organized to fulfill adult- or child-related motor tasks that can be evaluated by the time required to perform them (timed tests), the way they are performed, or the difficulty in performing them (scales and questionnaires). The best-validated observational functional test, which has also been used in therapeutic trials and is a CSM for JDM, is the Childhood Myositis Assessment Scale, which assesses muscle strength, observed function, and endurance[3,4,7]. The Functional Index-2 (FI-2), an observational measure of muscle fatigue in which patients perform repetitive movements in eleven proximal and distal muscle groups of the upper and lower extremities, has good construct and content validity and rater reliability in adult DM and PM[3,36]. It is being used as a secondary endpoint in DM/PM therapeutic trials[9,10]. FI-2 is well tolerated by patients, does not require expensive equipment, and unilateral FI-2 requires only 20 minutes to complete. Recently, a new hybrid measure of muscle strength and function—a composite of the MMT-8[36] and three items of the CMAS—was developed for JDM and validated using three large multinational cohorts[37].

In neuromuscular disorders, several timed tests have been used in therapeutic trials or observational studies to assess muscle function, endurance, and fatigability. In addition to the FI-2[3,38], they include the 2- and 6-minute walking distance test (2/6MWDT)[39], timed 10-meter walk/run test[40], timed up-and-go test (TUG)[39,41,42], 30-second chair stand test (30s-CST)[43,44], and Short Physical Performance Battery (SPPB)[45,46] (Table 4). Except for the 6MWDT, these tests have not been validated in adult or juvenile myositis. The 6MWDT has been widely used to assess gait performance and endurance capacity and was recently used as the primary endpoint in the (negative) bimagrumab therapeutic trial in IBM, the largest IBM trial to date[47]. In IBM, moderate correlation between the 2MWDT and the 6MWDT was shown, with the 2MWDT being more feasible and less onerous for patients[48]. The number of observational functional tests must be limited to avoid patient fatigue. They must be selected based on the patients' characteristics and must be highly standardized. For most of the functional tests, normative data exist, and results may be expressed as a

percentage of predicted normal values. Validated functional measures can be a strong secondary endpoint in myositis clinical trials or studies, especially in patients with baseline muscle weakness.

In contrast, questionnaires and scales that evaluate patients' or parents' self-report of performance of common functions of daily activities can be self-administrated or administered by an interviewer. Although functional questionnaires have significant advantages of feasibility and easy administration, they have the limitation of not directly assessing physical activity. These questionnaires will be discussed in the section on patient-reported outcome measures below (also see Supplementary Table 1).

Physical activity monitoring

Habitual physical activity can also be measured at home using accelerometers or other devices[49]. The use of accelerometry was recently pilot-tested in IIM[50]. A full validation study of 50 consecutive IIM patients is ongoing at two independent centers (Rohit Aggarwal and Olivier Benveniste, personal communication). Numerous variables, such as average daily step count and acceleration vector magnitude, can be used to describe the intensity, duration, and types of activities. Although physical activity monitoring has good face validity, further reliability and validity studies are needed in IIM. Major advantages of physical activity monitoring, if proven to be a reliable and valid outcome measure for IIM, are practicality, objectivity, continuous longitudinal monitoring, and lack of cognitive input from patient or examiner. However, interpretation of results must be performed, keeping in mind that the performance of physical activities depends mostly on behavioral factors, not only on motor capacities. A recent study showed poor agreement between actigraphy measurements and self-reported physical activity in JDM[33]. The patient must also be compliant to use the devices properly.

It is important that all tools specifically developed for adult patients are also validated in the pediatric setting, taking into account the motor and developmental issues that are specific to growing children. Children younger than 5 years of age often cannot cooperate for strength and observational functional assessment, and equipment sizes may need to vary for children of different ages.

Patient-reported outcomes

The value of incorporating the patient's perspective when conducting clinical research has been increasingly appreciated. Therapeutic trials and observational studies should include patient-reported outcome measures (PROMs), i.e., assessment of the outcomes that matter most to patients. However, many clinical assessment tools used for rheumatic diseases have been developed with limited or no patient involvement, and patients themselves largely have not evaluated existing PROMs for their relevance, feasibility, and validity. Furthermore, not all PROMs can be used for the same disease, given the heterogeneity of presentations and the variable impacts on patients. Thus, disease-specific PROMs are vital in helping to standardize clinical trial outcomes.

The currently available measurement tools for assessing PROMs in patients with myositis, including questionnaires that evaluate functional status, pain, fatigue, and HRQoL, are summarized in Supplementary Table 1. In terms of general questionnaire-based assessment of daily life activities that are not myositis specific, the HAQ (and the Childhood HAQ [CHAQ], which parents complete for pediatric patients) is a PROM that has eight functional domains, including dressing, arising, eating, walking, hygiene, reach, grip, and social activities, with a total of 20 functional task items. Patients self-report their functional level based on their level of difficulty in performing the task. The HAQ and CHAQ have been well-validated in DM, PM, and JDM; have been translated into multiple languages; and have been one of the CSMs used in PM/DM/JDM clinical trials[3,4,6,7,51].

HRQoL is a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning and is focused on how health status affects life quality. HRQoL is of particular relevance in IIM because, despite their improved prognosis with current treatment approaches, IIMs still have considerable impact on the HRQoL of patients[52,53]. PROMs have added valuable data on both treatment efficacy and QoL, which are immediately relevant to disease activity management[54]. A systematic review of published studies on HRQoL in myositis and a recent large North American registry study of adult IIM patients demonstrated that overall HRQoL is lower in all IIM subsets (DM, PM, and IBM) in comparison to both healthy populations and rheumatoid arthritis patients, and that active disease, higher damage score, and chronic illness are associated with poorer QoL[52,55]. Patients with JDM have significant impairment in their HRQoL compared with healthy peers, particularly in the physical domain, with physical well-being primarily affected by the level of functional impairment[53].

IMACS has recommended use of the Short Form-36 (SF-36) for adult IIM and Child Health Questionnaire-Parent Form 50 (CHQ-PF50) for JDM to assess HRQoL, although the latter is costly, and SF-36 has not been fully validated in this context[1,53,56]. The CHQ-PF50 physical summary score is one of the validated PRINTO JDM CSM with good responsiveness properties in clinical trials[4,7]. Strength has been shown to correlate with HRQoL in DM and PM[57], JDM[58], and IBM[59].

No myositis-specific PROM has been developed to date, but effort is ongoing through the Outcome Measures in Rheumatology Clinical Trials (OMERACT) consortium. OMERACT has brought healthcare providers, patients, and other stakeholders together to evaluate, develop, and validate PROM for adult myositis under a framework known as the Myositis Special Interest Group (SIG)[60–62]. The Myositis SIG has evaluated PROMs in myositis and neuromuscular studies and clinical trials according to the OMERACT filters of truth, discrimination, and feasibility (Supplementary Table 1)[60]. Review of the Myositis Activities Profile for DM/PM, one of the few myositis-specific, validated PROMs in which adult patients were involved in its development, indicated that, although content was deemed relevant and significant to patients, there were several limitations, including the perception that many questions were vague or ambiguous, and the dimensions of "difficulty" and "importance" were difficult to understand[61].

To assess the impact of myositis on patients' daily lives, the OMERACT Myositis SIG conducted semi-structured focus group interviews of DM and PM patients from three countries. The following five themes emerged as essential elements to capture in a future myositis-specific PROM—symptoms, activity/participation, strategies, knowledge of disease, and self-management and emotional factors[61]. From these focus group meetings, the top five rated domains included muscle symptoms, fatigue, interaction with healthcare and authorities, medication side effects, and pain.

Until the work of OMERACT has concluded, the recommendations from the European Neuro-Muscular Centre (ENMC) workshop on myositis outcome measures could be utilized[12], with consideration to include the SF-36 and/or Myositis Activities Profile as a PROM for adult DM/PM and the CHQ-PF50, which has been validated by PRINTO, for JDM[53]. For IBM, the disease-specific Sporadic Inclusion Body Myositis Physical Functioning Assessment[63,64], which was developed with patient involvement, and the Inclusion Body Myositis Functional Rating Scale (IBMFRS)[35,65], which was derived from the amyotrophic lateral sclerosis functional rating scale, are being used as endpoints in therapeutic trials[66]. Further work is needed to develop PROMs for IBM.

Other measures

Although individual CSM and combinations of them have been well validated as composite response criteria for clinical trials and studies in adult and juvenile DM and PM and are most frequently used as outcome measures in therapeutic trials, the CSM do not singularly assess certain aspects of disease that may be important in subgroups of patients. Additional clinical measures to assess skin disease activity and damage for patients with DM and JDM and pulmonary disease for patients with interstitial lung disease (ILD) have been developed and partially validated for DM, JDM, and PM[3,12]. Consensus has been obtained by the ENMC outcome assessment working group to include the Cutaneous Dermatomyositis Disease Area and Severity Index to assess skin activity and damage across multiple body regions in DM. In DM/PM patients with ILD, consensus was reached to include the Myositis Disease Activity Assessment Tool, as well as the OMERACT consensus measures for connective tissue-associated ILD, including pulmonary function testing (forced vial capacity and diffusion capacity of lung for carbon monoxide), supplemental oxygen requirement, dyspnea scale ratings, and 6MWDT[12] as measures to evaluate this disease complication[67]. Progression-free survival or time to progression of ILD is recommended for consideration as a composite endpoint for clinical trials of connective tissue–associated ILD, with 10% decline in forced vial capacity associated with mortality in IIM[12,67]. The Swallowing Quality of Life questionnaire has been used to assess dysphagia in patients with IBM[68].

Disease state criteria

Disease state criteria are important as another type of measure of clinical response[14] (Table 5). With the advent of new therapies and treatment strategies for JDM[69], inactive disease has become a realistic therapeutic target for patients with JDM[70,71]. Using a data-driven approach from a large prospective JDM cohort, the PRINTO group developed criteria for clinically inactive disease (on or off therapy), which include three of the four CSMs

returning to normal or near-normal values, including creatine kinase (CK), CMAS, MMT, and PGA[72] (Table 5). Because residual rashes and nailfold capillary changes frequently remain after the muscle criteria of this definition are met, requiring the PGA to return to normal improves the positive predictive value of the criteria for inactive disease[73]. Criteria for inactive disease are not yet available for adult DM, PM, or IBM.

Clinically inactive disease is defined as a point in time with clinically and biologically quiescent disease, either on or off therapy. By using consensus methodology, IMACS has defined criteria for complete clinical response for DM, PM, JDM, and IBM as a   6-month continuous period with no evidence of disease activity while still receiving myositis therapy, compared to significant disease activity in the past, whereas clinical remission is defined as a   6-month continuous period of inactive disease while not receiving any myositis therapy[74]. These criteria are preliminary and proposed for JDM, adult DM, PM, and IBM, and have yet to be validated. The time to achieve clinical remission, as defined by   6 continuous months of clinically inactive disease (on or off therapy) has been reported as a secondary endpoint in a JDM therapeutic trial, but has not been validated as an endpoint[7].

IMACS has also defined, via consensus, preliminary criteria for flare or worsening, and PRINTO has defined flare criteria for JDM in the context of an endpoint in the new-onset JDM trial[7,74] (Table 5). Not only can these criteria be used as an outcome in therapeutic trials, but they can also be used to determine whether a patient is not responding to an experimental therapy and needs to be withdrawn from a trial. The PRINTO trial used the time to prednisone discontinuation as an additional secondary long-term outcome in order to account for the fact that corticosteroids are still the mainstay of treatment for JDM, despite their known adverse effects on growth and development[7].

Imaging

Imaging modalities may be useful in myositis outcome assessment as ancillary measures to the validated CSMs and response criteria by providing measures that are potentially more objective and by discriminating active disease from muscle damage. Magnetic resonance imaging (MRI) is the preferred muscle imaging modality. It can be used as a noninvasive tool to sensitively monitor disease activity and muscle damage in many muscle groups simultaneously without exposing the patient to ionizing radiation[75,76]. The ability of MRI to differentiate between acute and chronic muscle pathology makes it particularly useful. However, there is still no standardised and universally accepted MRI protocol or quantitative or qualitative scoring of MRI assessment in IIMs. In routine care, T2-weighted sequences with fat suppression, such as the short tau inversion recovery (STIR) sequence, are used to detect water deposition/muscle oedema as part of muscle inflammation, regeneration, and necrosis, whereas T1-weighted sequences are usually used to detect muscle atrophy and intramuscular fat accumulation or fibrosis as part of chronic changes[77]. MRI has also been used to clarify whether a patient is flaring and requires additional treatment or whether the muscle inflammation has resolved, supporting reduction in therapy[78].

Semi-quantitative and quantitative assessments by MRI have potential as outcome measures in IIM. Semi-quantitative MRI scoring systems use ordinal scales of varying range to assess

fatty infiltration of muscle and muscle oedema, and less frequently muscle atrophy, as well as perifascicular, subcutaneous, soft-tissue, and fascial oedema, but those scoring systems have not been standardised[79]. In studies using semi-quantitative scoring systems, total oedema and damage scores in muscle and fascia correlated with MMT and functional testing in patients with anti-synthetase syndrome[80], while muscle oedema correlated with PGA, muscle strength by MMT, and CK levels in PM/DM patients[81], and muscle fatty infiltration correlated with strength and function in IBM patients[82]. A review of MRI semi-quantitative and quantitative scoring methods used to evaluate muscle involvement in patients with IIM was recently published[79].

Quantitative MRI scoring systems use continuous scales of MRI parameters that reflect muscle composition and/or haemodynamic properties. The most frequently used quantitative muscle imaging methods are fat fraction (which quantifies tissue fat content on a 0–100% fat-fraction scale), transverse relaxation time (T2), and magnetisation transfer ratio. T2 and magnetisation transfer ratio are sensitive to changes in a muscle's water distribution and lipid content. In a recent prospective quantitative MRI study in patients with IBM, fat fraction of whole calf and thigh muscles (measured using MRI Dixon fat water imaging) increased significantly after 1 year (Figure 1) and correlated with the lower limb components of the IBMFRS[83]. That study demonstrated the validity and responsiveness of MRI outcome measures, particularly fat fraction, in IBM, suggesting that MRI biomarkers might prove valuable in therapeutic trials, with the potential to decrease sample size if used as the primary endpoint in early-phase clinical trials[83]. Another study of MRI quantitation in DM, PM, and JDM showed good construct validity of semi-quantitative STIR and T1 scores, as well as quantitative maps of T2, fat-corrected T2, and fat fraction of thigh muscles, with clinical disease activity and damage measures. The MRI scores were responsive to change in a subgroup of patients from the Rituximab in Myositis trial, but changes in these MRI measures did not agree well with the clinical response criteria, perhaps because the MRI quantitates only changes in muscle oedema[84].

Whole-body MRI is currently used at some centres and can provide a comprehensive picture of the distribution patterns of affected muscles and reveal clinically unsuspected involvement of distal or axial muscle groups, thereby offering advantages over regional imaging[85]. It can also detect associated cardiopulmonary disease, avascular necrosis, and malignancies[86]. However, it is still not widely available and is prone to fat-suppression artifacts. Other emerging, but still exploratory, imaging modalities include functional MRI, MR spectroscopy, as well as MR or ultrasound elastography, which are being evaluated in some subtypes of myositis[75,76]. Real-time MRI has shown potential for evaluating dysphagia in IBM[68]. Finally, total and appendicular lean body mass measured by dual-energy X-ray absorptiometry have been used as outcome measures in IBM clinical trials[47,66].

Biomarkers

Traditional biomarkers of IIM disease activity have included serum levels of CK and other muscle-related enzymes, and these are part of the CSMs. However, their relationship to disease activity is variable, especially in DM, IBM, and JDM, resulting in a great need for the development of more specific and sensitive biomarkers. Presently, we understand that

innate and adaptive immunity, as well as non-immune muscle-related mechanisms, are involved in IIM pathogenesis[87,88]. Genes and proteins related to immune activation are some of the many targets for new biomarkers in the IIMs. However, such studies often examine only a single biomarker of disease and have not been validated in longitudinal or multi-site studies and hence require confirmation. Immune activation results in cytokines, chemokines, and other proteins being secreted into serum or plasma when the disease is active (Table 6). These potential biomarkers were first proposed when gene expression and protein assays were developed, and they demonstrate how complex and matrixed the immune system is in the IIMs.

Cytokines, particularly interleukin-6 (IL-6), are dysregulated in the IIMs. Studies identified IL-6 expression in both immune and muscle cells in muscle tissue[88–92]. Serum IL-6 levels are significantly elevated in DM and JDM, and they correlate with disease activity at diagnosis, with ongoing disease changes after varying treatments, and with the presence of ILD.

T-cell biomarkers include those related to Th17 cells, such as IL-17 and IL-23, which are seen in muscle and serum of DM and JDM patients early in the disease course and correlate with active disease[88–91,93] (Table 6). Some are elevated in subgroups of patients, such as the cytokine B cell–activating factor, which is dysregulated in both serum and RNA in patients with DM, PM, and JDM, especially those with ILD, anti-Jo-1 autoantibodies, and active disease[91,94,95].

Type I interferon (IFN)-related cytokines and chemokines are upregulated in the muscle and blood of patients with DM and JDM who have active disease[88–92,96–100]. In the IIMs, type I IFN–regulated proteins are some of the most studied biomarkers related to disease activity and outcome. Specifically, CXCL10 (IP-10), CXCL11 (I-TAC), MCP-1, and IL-6 are strongly expressed in muscle, skin, peripheral blood, and CXCL10 in blood vessel endothelial cells, and correlate with measures of IIM disease activity, including cutaneous disease[101–104].

Other proposed biomarkers that derive from myeloid cells, adipokines, and innate immune receptors are elevated in active JDM and DM[90,96,105–111]. A macrophage and endothelial cell cytokine, IL-8, correlates with changes in global and muscle scores in adult patients with ILD (including those with anti-MDA5 autoantibody-associated ILD)[90,92,96,106]. Galectin-9, a novel disease marker recently described in JDM, correlates strongly with other markers, such as tumor necrosis factor receptor-2 and CXCL10, as well as with measures of disease activity and the need for ongoing treatment[108]. Krebs von den Lungen-6 is expressed in the lung and is elevated in serum of patients with DM-related ILD[110], and serum ferritin is also elevated in DM/PM patients with ILD and is a predictor of survival[112]. Immune-mediated necrotizing myopathy, a recently recognized subgroup of IIM, has a strong Th1 cell response in the muscle tissue, which may inform the identification of future biomarkers and aid in diagnostic decisions[113].

Myositis-specific autoantibodies (MSAs) are increasingly recognized in all forms of IIM. Specific autoantibodies suggest IIM subtype as well as the development of distinct clinical

features and outcomes[114,115] (cross reference Review on Myositis Autoantibodies in this focus issue) (Table 6). MSA titres have been shown to be associated with disease activity, and serum levels decrease after therapy in many cases[116–118]. Similarly, decreases in anti-MDA5 autoantibody levels have been associated with longer remission, and increased levels have been associated with relapses[119,120]. Higher MSA titres have also been associated with poorer outcomes, as in the association of high titres of anti-MDA5 autoantibodies with rapidly progressive ILD[121].

Many of these biomarkers have been studied in clinical trials, including in the Rituximab in Myositis trial[6], where correlations were found between improvement in the IFN-chemokine score and improvement in global and specific measures of disease activity, as well among certain MSAs[90,99]. MSA titres also declined after rituximab therapy and correlated with changes in disease activity measures[116]. Specifically, the serum levels of anti-Jo-1, TIF-1 gamma, and Mi-2 decreased after rituximab and showed moderate to strong correlation with most disease activity measures. ~~Suppression~~ Reduction in the IFN gene score in blood and muscle correlated with clinical improvement in muscle strength in a trial of an anti-IFNα monoclonal antibody, as well as in the rituximab trial[122,123].

On occasion, serial muscle biopsies have been used to assess treatment effects in the IIM, particularly to examine specific biomarkers[9,10,122,123]. A score tool for assessing the histological severity of involved muscle has been validated in JDM but not in other IIM[124]. However, the utility of outcome assessment with histological biomarkers is limited by the invasiveness of the biopsy procedure and lack of validation of a score tool beyond JDM.

Conclusions

The development and dissemination of many validated outcome assessment measures for myositis activity and damage has brought standardisation to the field, which has aided in our understanding of long-term outcomes of these diseases and in developing and evaluating new therapies. The new myositis response criteria for DM, PM, and JDM should provide a more robust and sensitive composite endpoint to detect clinical responses of different magnitudes. Additional measures of muscle strength and function, as well as the assessment of other target organs and HRQoL, require further development and validation but show promise in bringing forward new tools with good content and construct validity. Such measures may also be used as endpoints in trials, including potentially as part of future composite response criteria, in studies of specific organ manifestations (such as skin or pulmonary disease), or for a particular subgroup of patients. Imaging and biomarkers are objective measures that can discriminate disease activity from damage, but they need to be standardised and further evaluated for the effects of therapies and sensitivity to change. We envision use of the core set measures and the response criteria as central to outcome assessment in all myositis therapeutic trials, which will facilitate international use, standardisation of endpoints, and comparisons between studies, therapies, and patient subgroups, and may be applied in the clinic to guide therapeutic decisions. Further development of additional measures may result in a targeted assessment of specific disease features to augment the core set measures. We envision future development of additional measures and indices that may be more sensitive and objective, as well as the gathering of

real-time, real-life data from patients through smart-phone applications and actigraphy that may augment our current targeted clinical assessments. Finally, the various outcome measures are often presented as competing, but they should be considered as complementary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Glossary

Core set measures

Minimum set of validated assessments that are recommended to be used in therapeutic trials and natural history studies.

Response criteria

A set of conditions, usually involving combinations of assessment tools, that defines clinically important improvement in disease symptoms and signs, which allows investigators, clinicians, regulators, and patients to determine the efficacy (or lack thereof) of a given therapeutic intervention and enables all of those persons to communicate about response to treatment by using the same metric.

Manual muscle testing

A method for assessing the strength of individual muscle groups based on the performance of a movement in relation to the forces of gravity and manual resistance by the examiner.

Dynamometer

A device that measures muscle strength during muscle contraction, such as gripping, pushing, and pulling.

Patient-reported outcome measures (PROMs)

A measurement based on information provided directly by the patient (i.e., study subject) about the status of his/her health condition, without amendment or interpretation of the patient's response by a clinician or anyone else.

Health-related quality of life (HRQoL)

A multidimensional assessment of a subject's health that includes domains related to physical, mental, emotional, and social functioning. It goes beyond direct measures of health, life expectancy, and causes of death, and focuses on the impact that health status has on quality of life.

Magnetic resonance imaging (MRI)

An imaging technique that uses a magnetic field and radio waves to create detailed images of the organs and tissues within the body.

Biomarker

A measurable indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

References

1. Miller FW et al. for the International Myositis Outcome Assessment Collaborative Study Group. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford) 40, 1262–1273 (2001). [PubMed: 11709610]

2. Ruperto N & Martini A Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch. Dis. Child 96, 596–601 (2011). [PubMed: 21317432]

3. Rider LG et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), Physician Global Damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res. (Hoboken.) 63 Suppl 11, S118–S157 (2011). [PubMed: 22588740]

4. Ruperto N et al. The provisional Paediatric Rheumatology International Trials Organisation/ American College of Rheumatology/European League Against Rheumatism Disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. Arthritis Rheum 59, 4–13 (2008). [PubMed: 18163404]

5. Rose MR 188th ENMC International Workshop: Inclusion Body Myositis, 2–4 December 2011, Naarden, The Netherlands. Neuromuscul. Disord 23, 1044–1055 (2013). [PubMed: 24268584]

6. Oddis CV et al. and the Rituximab in Myositis (RIM) Study Group. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 65, 314–324 (2013). [PubMed: 23124935]

7. Ruperto N et al. Paediatric Rheumatology International Trials Organisation (PRINTO). Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. Lancet 387, 671–678 (2016). [PubMed: 26645190]

8. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. Ann. Neurol 70, 427–436 (2011). [PubMed: 21688301]

9. Zong M et al. Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. Ann. Rheum. Dis 73, 913–920 (2014). [PubMed: 23625983]

10. Tjarnlund A et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. Ann. Rheum. Dis 77, 55–62 (2018). [PubMed: 28993346]

11. Rider LG et al. the International Myositis Assessment and Clinical Studies Group and the Paediatric Rheumatology International Trials Organisation. 2016 ACR-EULAR adult dermatomyositis and polymyositis and juvenile dermatomyositis response criteria-methodological aspects. Rheumatology (Oxford) 56, 1884–1893 (2017). [PubMed: 28977549]

12. Benveniste O & Rider LG ENMC Myositis Outcomes Study Group. 213th ENMC International Workshop: Outcome measures and clinical trial readiness in idiopathic inflammatory myopathies, Heemskerk, The Netherlands, 18–20 September 2015. Neuromuscul. Disord 26, 523–534 (2016). [PubMed: 27312023]

13. McCann LJ et al. The development of an optimal core dataset in juvenile dermatomyositis for clinical use to inform research. Ann. Rheum. Dis (In press).

14. Singh JA et al. Development of classification and response criteria for rheumatic diseases. Arthritis Rheum 55, 348–352 (2006). [PubMed: 16739201]

15. Rider LG et al. International Myositis Assesment and Clinical Studies Group. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum 50, 2281–2290 (2004). [PubMed: 15248228]

16. Ruperto N et al. The Pediatric Rheumatology International Trials Organization provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. Arthritis Care Res. (Hoboken) 62, 1533–1541 (2010). [PubMed: 20583105]

17. Hansen P & Ombler F A new method for scoring additive multi-attribute value models using pairwise rankings of alternatives. J. Multi-Crit. Decis. Anal 15, 87–107 (2008).

18. van den Hoogen F et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 65, 2737–2747 (2013). [PubMed: 24122180]

19. Neogi T et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatol 67, 2557–2568 (2015). [PubMed: 26352873]

20. Neogi T et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum 62, 2582–2591 (2010). [PubMed: 20872596]

21. de Lautour H et al. Development of preliminary remission criteria for gout using Delphi and 1000Minds consensus exercises. Arthritis Care Res. (Hoboken) 68, 667–672 (2016). [PubMed: 26414176]

22. Aggarwal R 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 69, 898–910 (2017). [PubMed: 28382787]

23. Rider LG et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in juvenile dermatomyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation collaborative initiative. Arthritis Rheumatol 69, 911–923 (2017). [PubMed: 28382778]

24. Aggarwal R 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. Ann. Rheum. Dis 76, 792–801 (2017). [PubMed: 28385805]

25. Rider LG et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in juvenile dermatomyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation collaborative initiative. Ann. Rheum. Dis 76, 782–791 (2017). [PubMed: 28385804]

26. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum 57, 193–202 (2007). [PubMed: 17330293]

27. Harris-Love MO et al. Distribution and severity of weakness among patients with polymyositis, dermatomyositis and juvenile dermatomyositis. Rheumatology (Oxford) 48, 134–139 (2009). [PubMed: 19074186]

28. Hogrel JY et al. Four-year longitudinal study of clinical and functional endpoints in sporadic inclusion body myositis: implications for therapeutic trials. Neuromuscul. Disord 24, 604–610 (2014). [PubMed: 24857365]

29. Allenbach Y et al. Quadriceps strength is a sensitive marker of disease progression in sporadic inclusion body myositis. Neuromuscul. Disord 22, 980–986 (2012). [PubMed: 22738680]

30. Albayda J et al. Dermatomyositis patients with anti-nuclear matrix protein-2 autoantibodies have more edema, more severe muscle disease, and increased malignancy risk. Arthritis Care Res. (Hoboken) (2017).

31. Pinal-Fernandez I et al. Longitudinal course of disease in a large cohort of myositis patients with autoantibodies recognizing the signal recognition particle. Arthritis Care Res. (Hoboken) 69, 263–270 (2017). [PubMed: 27111848]

32. Rider LG et al. International Myositis Assessment and Clinical Studies Group. Defining clinical improvement in adult and juvenile myositis. J. Rheumatol 30, 603–617 (2003). [PubMed: 12610824]

33. Pinto AJ et al. Poor agreement of objectively measured and self-reported physical activity in juvenile dermatomyositis and juvenile systemic lupus erythematosus. Clin. Rheumatol 35, 1507–1514 (2016). [PubMed: 27021334]

34. Rider LG et al. Novel assessment tools to evaluate clinical and laboratory responses in a subset of patients enrolled in the Rituximab in Myositis trial. Clin. Exp. Rheumatol 32, 689–696 (2014). [PubMed: 25068290]

35. Cortese A et al. Longitudinal observational study of sporadic inclusion body myositis: implications for clinical trials. Neuromuscul. Disord 23, 404–412 (2013). [PubMed: 23489664]

36. Rider LG et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. Arthritis Care Res. (Hoboken) 62, 465–472 (2010). [PubMed: 20391500]

37. Varnier GC et al. Development and testing of a hybrid measure of muscle strength in juvenile dermatomyositis for use in routine care. Arthritis Care Res. (Hoboken) (2017).

38. Alexanderson H et al. Functional index-2: Validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum 55, 114–122 (2006). [PubMed: 16463422]

39. Lowes LP et al. Knee extensor strength exhibits potential to predict function in sporadic inclusion-body myositis. Muscle Nerve 45, 163–168 (2012). [PubMed: 22246869]

40. Watson MJ Refining the ten-metre walking test for use with neurologically impaired people. Physiotherapy 88, 386–397 (2002).

41. Podsiadlo D & Richardson S The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J. Am. Geriatr. Soc 39, 142–148 (1991). [PubMed: 1991946]

42. Jorgensen AN et al. Physical function and muscle strength in sporadic inclusion body myositis. Muscle Nerve (2017).

43. McCarthy EK, Horvat MA, Holtsberg PA & Wisenbaker JM Repeated chair stands as a measure of lower limb strength in sexagenarian women. J. Gerontol. A Biol. Sci. Med. Sci 59, 1207–1212 (2004). [PubMed: 15602077]

44. Agarwal S & Kiely PD Two simple, reliable and valid tests of proximal muscle function, and their application to the management of idiopathic inflammatory myositis. Rheumatology (Oxford) 45, 874–879 (2006). [PubMed: 16449366]

45. Freire AN, Guerra RO, Alvarado B, Guralnik JM & Zunzunegui MV Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. J. Aging Health 24, 863–878 (2012). [PubMed: 22422762]

46. Ostir GV, Volpato S, Fried LP, Chaves P & Guralnik JM Reliability and sensitivity to change assessed for a summary measure of lower body function: results from the Women's Health and Aging Study. J. Clin. Epidemiol 55, 916–921 (2002). [PubMed: 12393080]

47. Amato AA et al. A randomized, double-blind, placebo-controlled study of bimagrumab in patients with sporadic inclusion body myositis. Arthritis Rheumatol 68 (Suppl 10) (2016).

48. Alfano LN et al. The 2-min walk test is sufficient for evaluating walking abilities in sporadic inclusion body myositis. Neuromuscul. Disord 24, 222–226 (2014). [PubMed: 24342281]

49. Jimenez-Moreno AC et al. Measuring habitual physical activity in neuromuscular disorders: A systematic review. J. Neuromuscul. Dis 4, 25–52 (2017). [PubMed: 28269791]

50. Bachasson D, Landon-Cardinal O, Benveniste O, Hogrel JY & Allenbach Y Physical activity monitoring: A promising outcome measure in idiopathic inflammatory myopathies. Neurology 89, 101–103 (2017). [PubMed: 28566549]

51. Ruperto N et al. for the Paediatric Rheumatology International Trials, Organisation. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin. Exp. Rheumatol 19 (Suppl. 23), S1–S9 (2001).

52. Leclair V, Regardt M, Wojcik S & Hudson M Canadian Inflammatory Myopathy Study (CIMS). Health-related quality of life (HRQoL) in idiopathic inflammatory myopathy: A systematic review. PLoS One 11, e0160753 (2016). [PubMed: 27504827]

53. Apaz MT et al. Health-related quality of life of patients with juvenile dermatomyositis: results from the Pediatric Rheumatology International Trials Organisation multinational quality of life cohort study. Arthritis Rheum 61, 509–517 (2009). [PubMed: 19333974]

54. van Tuyl LHD & Boers M Patient-reported outcomes in core domain sets for rheumatic diseases. Nat. Rev. Rheumatol 11, 705–712 (2015). [PubMed: 26324860]

55. Feldon M et al. Predictors of reduced health-related quality of life in adult patients with idiopathic inflammatory myopathies. Arthritis Care Res. (Hoboken) (2017).

56. Guyatt GH, Feeny DH & Patrick DL Measuring health-related quality of life. Ann. Intern. Med 118, 622–629 (1993). [PubMed: 8452328]

57. Poulsen KB et al. Quality of life correlates with muscle strength in patients with dermato- or polymyositis. Clin. Rheumatol (2017).

58. Takken T et al. The physiological and physical determinants of functional ability measures in children with juvenile dermatomyositis. Rheumatology.(Oxford) 42, 591–595 (2003). [PubMed: 12649408]

59. Sadjadi R & Rose MR What determines quality of life in inclusion body myositis? J. Neurol. Neurosurg. Psychiatry 81, 1164–1166 (2010). [PubMed: 20601666]

60. Alexanderson H et al. Patient-reported outcomes and adult patients' disease experience in the idiopathic inflammatory myopathies. report from the OMERACT 11 Myositis Special Interest Group. J. Rheumatol 41, 581–592 (2014). [PubMed: 24429182]

61. Regardt M et al. Patients' experience of myositis and further validation of a myositis-specific patient reported outcome measure - establishing core domains and expanding patient input on clinical assessment in myositis. Report from OMERACT 12. J. Rheumatol 42, 2492–2495 (2015). [PubMed: 25934817]

62. Park JK et al. Advancing the development of patient-reported outcomes for adult myositis at OMERACT 2016: An international delphi study. J. Rheumatol (2017).

63. DeMuro C et al. Development of the sporadic inclusion body myositis physical functioning assessment. Muscle Nerve 54, 653–657 (2016). [PubMed: 26872556]

64. Williams V et al. Psychometric validation of a patient-reported measure of physical functioning in sporadic inclusion body myositis. Muscle Nerve 54, 658–665 (2016). [PubMed: 26872636]

65. Jackson CE, Barohn RJ, Gronseth G, Pandya S & Herbelin L Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve 37, 473–476 (2008). [PubMed: 18236463]

66. Ahmed M et al. Targeting protein homeostasis in sporadic inclusion body myositis. Sci. Transl. Med 8, 331ra341 (2016).

67. Saketkoo LA et al. Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. Thorax 69, 428–436 (2014). [PubMed: 24368713]

68. Olthoff A et al. Evaluation of dysphagia by novel real-time MRI. Neurology 87, 2132–2138 (2016). [PubMed: 27770070]

69. Hasija R et al. Therapeutic approaches in the treatment of juvenile dermatomyositis in patients with recent-onset disease and in those experiencing disease flare: an international multicenter PRINTO study. Arthritis Rheum 63, 3142–3152 (2011). [PubMed: 21647864]

70. Feldman BM, Rider LG, Reed AM & Pachman LM Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 371, 2201–2212 (2008). [PubMed: 18586175]

71. Kim S et al. Complete and sustained remission of juvenile dermatomyositis resulting from aggressive treatment. Arthritis Rheum 60, 1825–1830 (2009). [PubMed: 19479872]

72. Lazarevic D et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Ann. Rheum. Dis 72, 686–693 (2013). [PubMed: 22736096]

73. Almeida B et al. Analysis of published criteria for clinically inactive disease in a large juvenile dermatomyositis cohort shows that skin disease is underestimated. Arthritis Rheumatol 67, 2495–2502 (2015). [PubMed: 25988361]

74. Oddis CV et al. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum 52, 2607–2615 (2005). [PubMed: 16142757]

75. Day J, Patel S & Limaye V The role of magnetic resonance imaging techniques in evaluation and management of the idiopathic inflammatory myopathies. Semin. Arthritis Rheum 46, 642–649 (2017). [PubMed: 28088340]

76. Filli L, Winklhofer S, Andreisek G & Del Grande F Imaging of myopathies. Radiol. Clin. North Am 55, 1055–1070 (2017). [PubMed: 28774448]

77. Adams EM, Chow CK, Premkumar A & Plotz PH The idiopathic inflammatory myopathies: spectrum of MR imaging findings. Radiographics 15, 563–574 (1995). [PubMed: 7624563]

78. Abdul-Aziz R et al. Muscle MRI at the time of questionable disease flares in juvenile dermatomyositis (JDM). Pediatr. Rheumatol. Online J 15, 25 (2017). [PubMed: 28403889]

79. Kubinova K, Mann H & Vencovsky J MRI scoring methods used in evaluation of muscle involvement in patients with idiopathic inflammatory myopathies. Curr. Opin. Rheumatol 29, 623–631 (2017). [PubMed: 28796007]

80. Andersson H et al. Comparative analyses of muscle MRI and muscular function in anti-synthetase syndrome patients and matched controls: a cross-sectional study. Arthritis Res. Ther 19, 17 (2017). [PubMed: 28122635]

81. Barsotti S et al. Thigh magnetic resonance imaging for the evaluation of disease activity in patients with idiopathic inflammatory myopathies followed in a single center. Muscle Nerve 54, 666–672 (2016). [PubMed: 27279002]

82. Guimaraes JB et al. Sporadic inclusion body myositis: MRI findings and correlation with clinical and functional parameters. AJR Am. J. Roentgenol, W1–8 (2017).

83. Morrow JM et al. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol 15, 65–77 (2016). [PubMed: 26549782]

84. Yao L et al. Magnetic resonance measurement of muscle T2, fat-corrected T2 and fat fraction in the assessment of idiopathic inflammatory myopathies. Rheumatology (Oxford) 55, 441–449 (2016). [PubMed: 26412808]

85. Malattia C et al. MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis. Ann. Rheum. Dis 72, 363–368 (2013). [PubMed: 22764042]

86. Huang ZG et al. An efficacy analysis of whole-body magnetic resonance imaging in the diagnosis and follow-up of polymyositis and dermatomyositis. PLoS One 12, e0181069 (2017). [PubMed: 28715432]

87. Manole E, Bastian AE, Butoianu N & Goebel HH Myositis non-inflammatory mechanisms: An updated review. J. Immunoassay Immunochem 38, 115–126 (2017). [PubMed: 28375073]

88. Olazagasti JM, Niewold TB & Reed AM Immunological biomarkers in dermatomyositis. Curr. Rheumatol. Rep 17, 68 (2015). [PubMed: 26404949]

89. Reed AM et al. Changes in novel biomarkers of disease activity in juvenile and adult dermatomyositis are sensitive biomarkers of disease course. Arthritis Rheum 64, 4078–4086 (2012). [PubMed: 22886447]

90. Lopez De Padilla CM et al. Interferon-regulated chemokine score associated with improvement in disease activity in refractory myositis patients treated with rituximab. Clin. Exp. Rheumatol 33, 655–663 (2015). [PubMed: 26446265]

91. Lopez de Padilla CM et al. BAFF expression correlates with idiopathic inflammatory myopathy disease activity measures and autoantibodies. J. Rheumatol 40, 294–302 (2013). [PubMed: 23322463]

92. Gono T et al. Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology (Oxford) 53, 2196–2203 (2014). [PubMed: 24970922]

93. Lopez De Padilla CM et al. Gene expression profiling in blood and affected muscle tissues reveals differential activation pathways in patients with new-onset juvenile and adult dermatomyositis. J. Rheumatol 44, 117–124 (2017). [PubMed: 27803134]

94. Kobayashi N et al. Increased serum B cell activating factor and a proliferation-inducing ligand are associated with interstitial lung disease in patients with juvenile dermatomyositis. J. Rheumatol 42, 2412–2418 (2015). [PubMed: 26472413]

95. Krystufkova O et al. Increased serum levels of B cell activating factor (BAFF) in subsets of patients with idiopathic inflammatory myopathies. Ann. Rheum. Dis 68, 836–843 (2009). [PubMed: 18628284]

96. De Bleecker JL, De Paepe B, Vanwalleghem IE & Schroder JM Differential expression of chemokines in inflammatory myopathies. Neurology 58, 1779–1785 (2002). [PubMed: 12084877]

97. O'Connor KA, Abbott KA, Sabin B, Kuroda M & Pachman LM MxA gene expression in juvenile dermatomyositis peripheral blood mononuclear cells: association with muscle involvement. Clin. Immunol 120, 319–325 (2006). [PubMed: 16859997]

98. Greenberg SA et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann. Neurol 57, 664–678 (2005). [PubMed: 15852401]

99. Reed AM et al. RIM Study Group. Biologic predictors of clinical improvement in rituximab-treated refractory myositis. BMC Musculoskelet. Disord 16, 257 (2015). [PubMed: 26382217]

100. Nara M et al. Serum interleukin 6 levels as a useful prognostic predictor of clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease. Mod. Rheumatol 24, 633–636 (2014). [PubMed: 24252021]

101. Baechler EC et al. An interferon signature in the peripheral blood of dermatomyositis patients is associated with disease activity. Mol. Med 13, 59–68 (2007). [PubMed: 17515957]

102. Huard C et al. Correlation of cutaneous disease activity with type 1 interferon gene signature and interferon beta in dermatomyositis. Br. J. Dermatol 176, 1224–1230 (2017). [PubMed: 27564228]

103. Shrestha S et al. Lesional and nonlesional skin from patients with untreated juvenile dermatomyositis displays increased numbers of mast cells and mature plasmacytoid dendritic cells. Arthritis Rheum 62, 2813–2822 (2010). [PubMed: 20506305]

104. Walsh RJ et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. Arthritis Rheum 56, 3784–3792 (2007). [PubMed: 17968926]

105. Nistala K et al. Myeloid related protein induces muscle derived inflammatory mediators in juvenile dermatomyositis. Arthritis Res. Ther 15, R131 (2013). [PubMed: 24286299]

106. Zou J, Chen J, Yan Q, Guo Q & Bao C Serum IL8 and mRNA level of CD11b in circulating neutrophils are increased in clinically amyopathic dermatomyositis with active interstitial lung disease. Clin. Rheumatol 35, 117–125 (2016). [PubMed: 26459323]

107. Yuan L et al. Serum levels of soluble ST2 and interleukin-33 in patients with dermatomyositis and polymyositis. Clin. Exp. Rheumatol 31, 428–432 (2013). [PubMed: 23485578]

108. Bellutti Enders F et al. Correlation of CXCL10, tumor necrosis factor receptor type II, and galectin 9 with disease activity in juvenile dermatomyositis. Arthritis Rheumatol 66, 2281–2289 (2014). [PubMed: 24756983]

109. Olazagasti JM et al. Adipokine gene expression in peripheral blood of adult and juvenile dermatomyositis patients and their relation to clinical parameters and disease activity measures. J. Inflamm 12, 29 (2015).

110. Bandoh S et al. Sequential changes of KL-6 in sera of patients with interstitial pneumonia associated with polymyositis/dermatomyositis. Ann. Rheum. Dis 59, 257–262 (2000). [PubMed: 10733471]

111. Sanner H et al. Increased levels of eotaxin and MCP-1 in juvenile dermatomyositis median 16.8 years after disease onset; associations with disease activity, duration and organ damage. PLoS One 9, e92171 (2014). [PubMed: 24647150]

112. Ishizuka M et al. Long-term follow-up of 124 patients with polymyositis and dermatomyositis: Statistical analysis of prognostic factors. Mod. Rheumatol 26, 115–120 (2016). [PubMed: 26011440]

113. Preusse C et al. Immune-mediated necrotizing myopathy is characterized by a specific Th1-M1 polarized immune profile. Am. J. Pathol 181, 2161–2171 (2012). [PubMed: 23058368]

114. Betteridge Z & McHugh N Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. J. Intern. Med 280, 8–23 (2016). [PubMed: 26602539]

115. Rider LG & Nistala K The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. J. Intern. Med 280, 24–38 (2016). [PubMed: 27028907]

116. Aggarwal R et al. Autoantibody levels in myositis patients correlate with clinical response during B cell depletion with rituximab. Rheumatology (Oxford) 55, 991–999 (2016). [PubMed: 26888854]

117. Aggarwal R et al. Anti-signal recognition particle autoantibody ELISA validation and clinical associations. Rheumatology (Oxford) 54, 1194–1199 (2015). [PubMed: 25524922]

118. Stone KB et al. Anti-Jo-1 antibody levels correlate with disease activity in idiopathic inflammatory myopathy. Arthritis Rheum 56, 3125–3131 (2007). [PubMed: 17763431]

119. Matsushita T et al. Antimelanoma differentiation-associated protein 5 antibody level is a novel tool for monitoring disease activity in rapidly progressive interstitial lung disease with dermatomyositis. Br. J. Dermatol 176, 395–402 (2017). [PubMed: 27452897]

120. Aggarwal R et al. Autoantibody levels in myositis patients correlate with clinical response during B cell depletion with rituximab. Rheumatology (Oxford) 55, 1710 (2016). [PubMed: 27383242]

121. Kobayashi N et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. Rheumatology (Oxford) 54, 784–791 (2015). [PubMed: 25288783]

122. Higgs BW et al. A phase 1b clinical trial evaluating sifalimumab, an anti-IFN-alpha monoclonal antibody, shows target neutralisation of a type I IFN signature in blood of dermatomyositis and polymyositis patients. Ann. Rheum. Dis 73, 256–262 (2014). [PubMed: 23434567]

123. Nagaraju K et al. Muscle myeloid type I interferon gene expression may predict therapeutic responses to rituximab in myositis patients. Rheumatology (Oxford) 55, 1673–1680 (2016). [PubMed: 27215813]

124. Varsani H et al. Validation of a score tool for measurement of histological severity in juvenile dermatomyositis and association with clinical severity of disease. Ann. Rheum. Dis 74, 204–210 (2015). [PubMed: 24064003]

125. Ruperto N et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. Rheumatology (Oxford) 42, 1452–1459 (2003). [PubMed: 12832713]

126. Beenakker EAC, van der Hoeven JH, Fock JM & Maurits NM Reference values of maximum isometric muscle force obtained in 270 children aged 4 – 16 years by hand-held dynamometry. Neuromuscul. Disord 11, 441–446 (2001). [PubMed: 11404114]

127. McKay MJ et al. Normative reference values for strength and flexibility of 1,000 children and adults. Neurology 88, 36–43 (2017). [PubMed: 27881628]

128. Bohannon RW Literature reporting normative data for muscle strength measured by hand-held dynamometry: a systematic review. Isokinet. Exerc. Sci 19, 143–147 (2011).

129. Hogrel JY et al. Development of a French isometric strength normative database for adults using quantitative muscle testing. Arch. Phys. Med. Rehabil 88, 1289–1297 (2007). [PubMed: 17908571]

130. Harbo T, Brincks J & Andersen H Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. Eur. J. Appl. Physiol 112, 267–275 (2012). [PubMed: 21537927]

131. Danneskiold-Samsoe B et al. Isokinetic and isometric muscle strength in a healthy population with special reference to age and gender. Acta Physiol. (Oxf.) 197 Suppl 673, 1–68 (2009).

132. Moraux A et al. Ankle dorsi- and plantar-flexion torques measured by dynamometry in healthy subjects from 5 to 80 years. BMC Musculoskelet. Disord 14, 104 (2013). [PubMed: 23522186]

133. Stoll T, Bruhlmann P, Stucki G, Seifert B & Michel BA Muscle strength assessment in polymyositis and dermatomyositis evaluation of the reliability and clinical use of a new, quantitative, easily applicable method. J. Rheumatol 22, 473–477 (1995). [PubMed: 7783064]

134. Mahler EA et al. Rituximab treatment in patients with refractory inflammatory myopathies. Rheumatology (Oxford) 50, 2206–2213 (2011). [PubMed: 21571768]

135. Cox FM et al. Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis. Rheumatology (Oxford) 50, 1153–1161 (2011). [PubMed: 21288962]

136. Lindberg C & Oldfors A Prognosis and prognostic factors in sporadic inclusion body myositis. Acta Neurol. Scand 125, 353–358 (2012). [PubMed: 21916852]

137. Alfano LN et al. Modeling functional decline over time in sporadic inclusion body myositis. Muscle Nerve 55, 526–531 (2017). [PubMed: 27511790]

138. Neri R et al. Functional and isokinetic assessment of muscle strength in patients with idiopathic inflammatory myopathies. Autoimmunity 39, 255–259 (2006). [PubMed: 16769660]

139. Benveniste O et al. Long-term observational study of sporadic inclusion body myositis. Brain 134, 3176–3184 (2011). [PubMed: 21994327]

140. Huber AM et al. Consensus treatments for moderate juvenile dermatomyositis: beyond the first two months. Results of the second Childhood Arthritis and Rheumatology Research Alliance consensus conference. Arthritis Care Res. (Hoboken) 64, 546–553 (2012). [PubMed: 22076847]

141. Yin L et al. The clinical utility of serum IL-35 in patients with polymyositis and dermatomyositis. Clin. Rheumatol 35, 2715–2721 (2016). [PubMed: 27502600]

142. Taylor KE et al. Risk alleles for systemic lupus erythematosus in a large case-control collection and associations with clinical subphenotypes. PLoS.Genet 7, e1001311 (2011). [PubMed: 21379322]

143. Tansley SL et al. Autoantibodies in juvenile-onset myositis: Their diagnostic value and associated clinical phenotype in a large UK cohort. J. Autoimmun (2017).

Key Points

- The primary assessment of myositis includes core set measures of disease activity, damage, and measures of patient-reported outcomes.

- A new composite myositis response criterion has been developed and validated; it combines and differentially weights core set activity measures to determine minimal, moderate, and major clinical response.

- Measures of muscle strength and function, including home monitoring of physical activity, are being refined for myositis subgroups and being used as primary or secondary outcome measures in myositis studies.

- Disease-specific patient-reported outcomes, including health-related quality-of-life measures that reflect patient perspectives, are being developed.

- Imaging and immunologic biomarkers provide objective measures that discriminate activity and damage, but they need to be validated in clinical trials.

Box 1.

Advantages and limitations of the 2016 ACR-EULAR response criteria for dermatomyositis, polymyositis, and juvenile dermatomyositis

Advantages	Limitations
• Weighted measures: CSMs are scored according to their relative weight of importance in defining disease activity • Continuous measure: provides a Total Improvement Score with continuous degree of improvement	• Some CSMs upon which the criteria are based are subjective and evaluator dependent
• Provides categorical outcomes: minimal, moderate, and major clinical response • Hybrid criteria: same criteria can be used either as continuous or categorical outcome	• Validation of the final criteria and thresholds for improvement were based on limited data
• Does not require minimal severity level in a myositis clinical trial at baseline in any CSM: all levels of improvement in CSMs contribute to the response	• The threshold for major response for adult DM/PM is preliminary: further data are needed to confirm it
• Changes based on absolute percentage change rather than relative percentage change in CSMs, which may be more realistic and have better face validity	• Fail to differentiate between no change and worsening • Cannot be used for disease flare or relapse • Does not define remission
• Same definition of improvement can be used for JDM, adult DM and PM, with different thresholds of minimal, moderate, and major improvement, allowing for combined JDM and adult DM/PM therapeutic trials	• Developed for major clinical phenotypes (DM, PM, JDM); no validation for other phenotypes (IMNM, anti-synthetase syndrome), but likely to work for these phenotypes as well • Difficult to use in everyday clinical practice without the use of a computer
• JDM response criteria allow possibility of using either the IMACS or PRINTO CSMs to define improvement	

Abbreviations: CSMs, core set measures; DM, dermatomyositis; IMACS, International Myositis Assessment and Clinical Studies Group; IMNM, immune-mediated necrotizing myopathy JDM, juvenile dermatomyositis, PM, polymyositis.
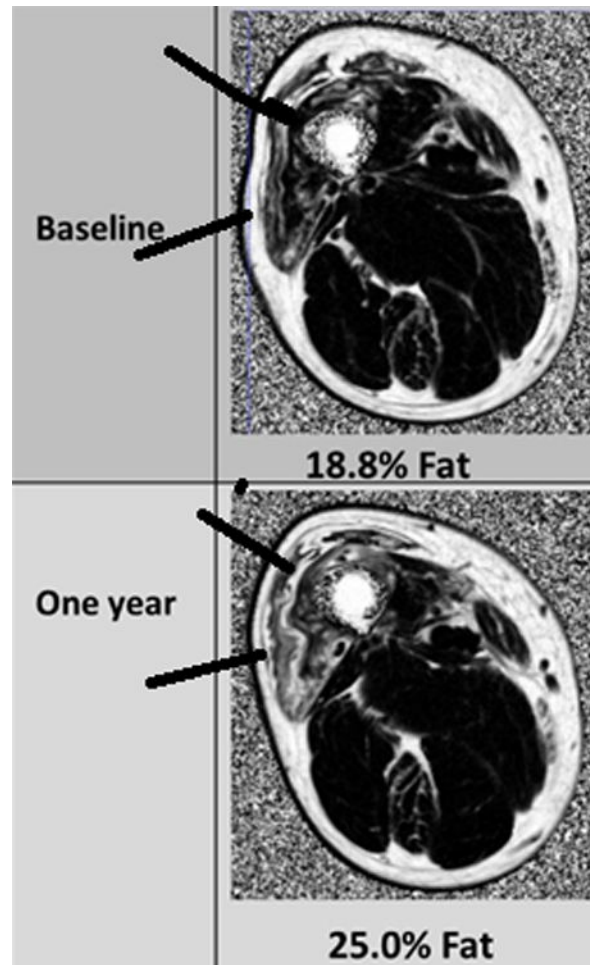
References: [11,22–25]

Figure 1.
Fat-fraction T1 magnetic resonance imaging (MRI) map in inclusion body myositis. Fat-fraction T1 MRI map of the right thigh in a patient with inclusion body myositis, at baseline and one-year follow-up. An absolute percentage increase of 6.2% in fat fraction was observed.

Table 1.

Core set measures for disease activity and damage assessment for clinical studies and therapeutic trials in adult and juvenile idiopathic inflammatory myopathies

Domain	Core set measure	IMACS core set measures for adult and juvenile DM, PM, IBM*	PRINTO core set measures for JDM
Disease Activity			
Physician global activity	Physician global disease activity assessment by Likert or visual analog scale	X†	X†
Patient/parent global activity	Patient/parent global disease activity assessment by Likert or visual analog scale	X†	X†
Muscle strength	1. MMT by 0–10 point or expanded 0–5-point scale to include proximal, distal, and axial muscles	X†	X
	2. CMAS		X (preferred)†
Physical function	1. Validated patient/parent questionnaire of activities of daily living (HAQ/CHAQ)	X†	X†
	2. CMAS	X	
Laboratory assessment	At least two serum muscle-associated enzyme activities from the following: creatine kinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, or alanine aminotransferase	X†	
Global disease activity, including extra-muscular disease activity	Myositis Disease Activity Assessment Tool to assess extramuscular organs, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac activity	X†	X
	DAS		X (preferred)†
Health-related quality of life	CHQ-PF50 Physical Summary Score		X†
Disease Damage			
Physician global damage	Physician global disease activity assessment by Likert or visual analog scale	X	X
Global damage tool	Myositis Damage Index	X	X
Physical function	Validated patient/parent questionnaire of activities of daily living (HAQ/CHAQ)	X	X
Muscle strength	CMAS		X
Growth and development	Height and weight, menses, Tanner puberty stage	X	X
Health-Related Quality of Life	SF-36 (adult)	X	
	CHQ-PF50 Physical Summary Score (PhS)	X	X

Modified from [1,4,125]

See http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm for copies of the tools, glossaries, training materials, and additional references.

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Abbreviations: CHAQ/HAQ, (Childhood) Health Assessment Questionnaire; CHQ-PF50, Child Health Questionnaire–Parent Form 50; CMAS, Childhood Myositis Assessment Scale; DAS, Disease Activity Score; DM, dermatomyositis; IBM, inclusion body myositis; IMACS, International Myositis Assessment and Clinical Studies Group; JDM, juvenile dermatomyositis; MMT, manual muscle test; PM, polymyositis; PRINTO, Pediatric Rheumatology International Trials Organization.

*
IMACS criteria are recommended for adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis, whereas PRINTO core set measures are recommended for juvenile dermatomyositis.

†
Included in the final core set activity measures used to develop the 2016 American College of Rheumatology/European Leagues Against Rheumatism criteria for minimal, moderate, and major improvement in adult dermatomyositis and polymyositis and juvenile dermatomyositis[22,23].

Table 2.

2016 American College of Rheumatology/European Leagues Against Rheumatism criteria for minimal, moderate, and major improvement in adult dermatomyositis and polymyositis and juvenile dermatomyositis

Core Set Measure[*]	Level of Improvement Based on absolute percentage change	Improvement Score
Physician Global Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	7.5
	>15% to 25% improvement	15
	>25% to 40% improvement	17.5
	>40% improvement	20
Patient or Parent Global Activity	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	10
Manual Muscle Testing or Childhood Myositis Assessment Scale	Worsening to 2% improvement	0
	>2% to 10% improvement	10
	>10% to 20% improvement	20
	>20% to 30% improvement	27.5
	>30% improvement	32.5
Health Assessment Questionnaire or Childhood Health Assessment Questionnaire	Worsening to 5% improvement	0
	>5% to 15% improvement	5
	>15% to 25% improvement	7.5
	>25% to 40% improvement	7.5
	>40% improvement	10
Enzyme (most abnormal) or CHQ-PhS	Worsening to 5% improvement	0
	>5% to 15% improvement	2.5
	>15% to 25% improvement	5
	>25% to 40% improvement	7.5
	>40% improvement	7.5

Core Set Measure[*]	Level of Improvement Based on absolute percentage change	Improvement Score
	Worsening to 5% improvement	0
	>5% to 15% improvement	7.5
Extramuscular activity or Disease Activity Score	>15% to 25% improvement	12.5
	>25% to 40% improvement	15
	>40% improvement	20

	Improvement category	Total improvement score[†]
	Minimal	20
DM/PM thresholds	Moderate	40
	Major	60
	Minimal	30
JDM thresholds	Moderate	45
	Major	70

Abbreviations: CHQ-PhS, Physical Summary Score of the Child Health Questionnaire-Parent Form 50; DM, dermatomyositis; Enzyme, most abnormal serum muscle enzyme level among creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase; JDM, juvenile dermatomyositis; PM, polymyositis.

[*]
Note that either all the IMACS or all the PRINTO core set measures may be used.

[†]
The total improvement score is the sum of all six improvement scores associated with the change in each core set measure.

Modified from [22–25].

Table 3.

Strength assessment methods The elements depicted are common features of various methodologies for muscle strength testing that are generally encountered in clinical protocols. The metrological properties of the equipment vary widely, depending on the devices used and their calibration. The pictures show examples of each method for ankle flexion assessment.

	Manual muscle testing (MMT)	Hand-held dynamometry (HHD)	Fixed dynamometry (QMT)	Isokinetic dynamometry	Specific dynamometry
Practicality	Very high	High	Moderate	Moderate	Moderate
Specific equipment and space required	No	Yes	Yes	Yes	Yes
Equipment cost	No cost or specialized equipment	Mildly expensive	Moderately expensive	Very expensive	Mildly expensive
Contraction conditions	Dynamic/static (depends on patient's abilities)	Isometric (make test) Pseudo-isometric (break test)	Isometric	Isometric Isokinetic Isotonic	Isometric
Time to administer (per muscle function)	<1 minute	<5 minutes	<5 minutes	5 minutes	5 minutes
Variable	Ordinal score (grade)	Best performance (kg)	Best performance (kg)	Best performance (Nm)	Best performance (kg or Nm)
Linearity	No	Yes	Yes	Yes	Yes
Resolution	Poor	Between 0.1 and 1 kg	Between 0.1 and 1 kg	Between 0.5 and 1 Nm	Between 0.001 and 0.1 kg
Accuracy	Limited	0.1–1% full scale	0.1–1% full scale	0.1–1% full scale	0.001–0.1% full scale
Adapted to weak patients	No	No	No	Possibly	Yes
Adapted to strong patients	No	No	Yes	Yes	Yes
Normative data exist[*]	NA	Yes[126-128]	Yes[129]	Yes[130,131]	Yes[132]

	Manual muscle testing (MMT)	Hand-held dynamometry (HHD)	Fixed dynamometry (QMT)	Isokinetic dynamometry	Specific dynamometry
Practicality	Very high	High	Moderate	Moderate	Moderate
Sensitivity to change	Poor in patients with mild weakness; moderate in weaker patients	Moderate	Moderate	High	High
Intra-rater reliability	Good	Good to excellent	Good to excellent	Good to excellent	Good to excellent
Inter-rater reliability	Moderate	Moderate to excellent	Good to excellent	Good to excellent	Good to excellent
Sensitivity to lever arm	Yes	Yes	Yes	No	Depends on the device
Floor/ceiling effects	Floor and ceiling effects	Floor effect	Floor effect	Floor effect	Limited
Composite scores	Yes	No (except if expressed as % normal values)	No (except if expressed as % normal values)	No (except if expressed as % normal values)	No (except if expressed as % normal values)
Use in myositis	IMACS core set measure; outcome measure in DM, PM, IBM and JDM therapeutic trials[1,3,6–8,10]	PM/DM[133,134]; JDM[58]; IBM[135]	IBM[35,39,136,137]	PM/DM/JDM[138]; IBM[28,29,35]	IBM[28,29]

Abbreviations: DM, dermatomyositis; IBM, inclusion body myositis; IMACS, International Myositis Assessment and Clinical Studies Group; JDM, juvenile dermatomyositis; NA, not applicable; PM, polymyositis.

*Normative data are given as predictive equations using age, sex, weight, and/or height.

The references given here are examples and are not exhaustive.

Table 4.

Observational functional or disability measures in myositis

Measure	Assessment and Description	Subgroups of myositis	Completion time (min)	Psychometric properties	Advantages	Limitations	References
CMAS	Muscle strength, function, and endurance in 14 items	JDM	15	Good reliability, construct validity, responsiveness	Comprehensive, examines strength, endurance, and function	Longer time to administer; significant ceiling effect	3,4
FI-2	Muscle endurance, assesses impairment of 11 muscle groups	PM, DM	30	Satisfactory construct validity and inter-rater and intra-rater reliability	No ceiling or floor effects and no redundant tasks, measures muscle endurance	Longer time to administer	3,38
2/6MWDT	Muscle strength and endurance	IBM	5/10	Valid and reliable in IBM, also used in muscle dystrophies	Simple and has been standardised in other diseases; recently used to support regulatory approval of neuromuscular drugs	Floor effect if weakness too severe; requires indoor course of adequate length	39
10 m walk/run	Muscle power	Populations with neurological conditions	<1	Unknown in myositis	Test can be done using normal comfortable speed or maximum speed trials	Not evaluated in myositis; variation regarding guidance to perform this test; floor effect if weakness too severe	40
TUG	Ability to rise from a chair as well as gait function (may need adaptations to allow patients to use their arms to stand up)	IBM	5	Good construct validity	A valid and reliable tool in frail and elderly subjects; simple and quick	Only assesses lower extremities and recorded time, not the patient's movements. The chair used can impact results.	39,41,42
30s-CST	Lower limb function. Patients are asked to rise from a standard-height chair and to sit down as many times as possible in 30 seconds.	PM, DM	<1	Good test-retest reliability	Simple and quick	Floor effect if weakness too severe; only assesses lower extremities. The chair used can impact results.	43,44
Short Physical Performance Battery	Lower limb function by using tests of gait speed, standing balance, and time to rise from a chair five times	IBM	<15	Excellent test-retest reliability	Provides useful qualitative information on the nature of mobility limitation	Longer time to administer	45,46
IBM Weakness Composite Index	Muscle strength and endurance	IBM	<15	Not tested yet	IBM specific		28,29,139

Abbreviations: 2/6MWDT, 2- and 6-minute walking distance test; 30s-CST, 30-second chair stand test; CMAS, Childhood Myositis Assessment Scale; DM, dermatomyositis FI-2, Functional Index-2; IBM, inclusion body myositis; TUG, timed up-and-go test.

Table 5.

Disease state criteria endpoints for potential use in therapeutic trials and clinical studies

Outcome measure/ endpoint	Definition or description	Applicable myositis subgroup(s)	Comments	References
Clinically inactive disease	At least 3 of 4 of the following criteria: creatine kinase 150 U/L, CMAS score 48 of 52, MMT-8 score 78 of 80, and Physician Global Activity 0.2 of 10 cm	JDM	PRINTO criteria. No definition exists for adult DM, PM, or IBM	72
Clinically inactive disease	Physician Global Activity of 0.2 of 10 cm AND at least 2 of the 3 following criteria: creatine kinase 150 U/L, CMAS score 48 of 52, and MMT-8 score 78 of 80	JDM	Modified PRINTO criteria. No definition exists for adult DM, PM, or IBM	73
Complete clinical response	6-month continuous period with no evidence of disease activity while still receiving myositis therapy	JDM, DM, PM, IBM	Consensus definition, not data driven	74
Remission	6-month continuous period with no evidence of disease activity while not receiving any myositis therapy	JDM, DM, PM, IBM	Consensus definition, not data driven	74
Clinical remission	6 continuous months of clinically inactive disease (on or off therapy)	JDM	PRINTO trial of new-onset JDM patients, utilized without validation	7
Disease flare or worsening criteria	1) Physician-assessed global worsening by 2 cm on a 10-cm VAS and worsening on MMT-8 by 20%; or 2) Extramuscular organ disease activity worsening by 2 cm on a 10-cm VAS; or 3) Any 3 of 6 IMACS CSMs worsening by 30%	JDM, DM, PM, IBM	Consensus definition, not data driven	74
Disease flare	20% worsening in any 2 of 6 CSMs, with no more than one of the remaining variables improving by >30% (muscle strength excluded).	JDM	PRINTO trial of new-onset JDM patients, utilized without validation	7
Corticosteroid discontinuation	Cessation of oral prednisone therapy	JDM	PRINTO trial of new-onset JDM patients. CARRA has proposed a standardized corticosteroid dose-reduction regimen based on consensus. Etanercept trial for adult DM also defines standardized steroid tapering regimen.	7,8,140

Abbreviations: CARRA, Childhood Arthritis and Rheumatology Research Alliance; CMAS, Childhood Myositis Assessment Scale; CSM, core set measure(s); DM, dermatomyositis; IBM, inclusion body myositis; IMACS, International Myositis Assessment and Clinical Studies Group; JDM, juvenile dermatomyositis; MMT-8, manual muscle testing on a subset of 8 muscles; PM, polymyositis; PRINTO, Paediatric Rheumatology International Trials Organisation; VAS, visual analog scale.

Table 6.

Biomarkers related to disease activity in the idiopathic inflammatory myopathies

Name	JDM	DM	PM	IMNM	ILD	References
IL-6	+++	++	+		+	88–91
T cell related markers						
Th-17 (IL–17 and IL–23)	+++	++				88–91
Th-2 (IL-4, IL_5, IL-10)		++	+			88,89
Th-1 (TNF-a, IL2, IFN-γ)			+	+ (IFN-γ, TNFα, IL-12, and STAT1)	+	88–91
IL-35					++ (DM/PM)	141
Type I IFN CCL2[MCP-1], CCL3, CCL4 [MIP1b], CCL8, CXCL9, CXCL10[IL-10], and CXCL11[I-TAC]), MxA	+++	++	+		+ (DM)	88–91,96–100
Myeloid and other related markers						
IL-8					++ (DM +MDA5)	90,96,106
IL-33/sST2		++				107
Galectin-9	+++					108
Adipokines	++	++				109
KL-6	+				++	110
MRP8/MRP14	+					105
BAFF	++	++	+			91,94,95
Eotaxin	+					111,142
Gene regulators (*GATA3, STAT6* and *STAT4*)	+ (*RORC*)	+ (*STAT3, BCL6*)				93
Myositis-specific autoantibodies (autoantibodies greater than 5% prevalence noted)	++ (TIF1*, NXP2, MDA5, Mi-2*, PM-Scl)	++ (TIF1γ*, Jo-1*, Mi-2*, SAE, MDA5, NXP2)	++ (TIF1γ*, Jo-1*, SRP, HMGCR, NXP2)	++ SRP, HMGCR	++ (Jo-1, MDA5, PL12)	114–116,143
Biomarkers in clinical trials	IL-8, MCP-1, IL-6, IL-1β, IL-13, IL-10, IL-2, and IFN-γ	IL-8, MCP-1, IL-6, IL-1β, IL-13, IL-10, IL-2, and IFN-γ	IL-8, MCP-1, IL-6, IL-1β, IL-13, IL-10, IL-2, and IFN-γ			

Abbreviations: BAFF, B cell–activating factor; BCL6, B-cell lymphoma 6; CCL, (C-C motif) ligand; cN1A, cytosolic 5'-nucleotidase 1A; CXCL, (C-X-C motif) ligand; DM, dermatomyositis; GATA3, GATA binding protein 3; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IBM, inclusion body myositis; IFN, interferon; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; IL, interleukin; I-TAC, interferon-inducible T-cell alpha chemoattractant; Jo-1, histidyl tRNA synthetase; KL-6, Krebs von den Lungen-6; MCP, monocyte chemoattractant protein; MDA5, melanoma differentiation-associated protein 5; MIP, macrophage inflammatory protein; MRP, myeloid-related protein; MxA, myxoma resistance protein; NXP2, nuclear matrix protein 2; PM, polymyositis;

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PM-Scl, polymyositis and scleroderma; RORC, RAR-related orphan receptor C; SAE, small ubiquitin like modifier activating enzyme heterodimer; SRP, signal recognition protein; STAT1, Signal transducer and activator of transcription 1; TIF1-γ, transcriptional intermediary factor 1 gamma; TNF, tumor necrosis factor.

(+) Represents level of evidence with 1–2 references (++), represents level of evidence with 2–5 reference; (+++) represents level of evidence with greater than 5 references; those left blank have little if any evidence.

*
changes with disease activity