Clinical endpoints in myositis: challenges and ways forward

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Purpose of review
This review addresses the challenges and advances in clinical endpoints for myositis, with a particular focus on ensuring comprehensive assessment of both muscle and skin disease activity. The relevance of this review stems from recent developments in outcome measures and their implications for clinical trial design and patient inclusivity. While quality of life (QoL) and lung involvement are also important aspects of myositis, they are beyond the scope of this review and need to be addressed in future studies.

Recent findings
Traditional outcome measures like the Total Improvement Score (TIS) have limitations, especially for patients with skin-predominant dermatomyositis (DM). Recent studies highlight the importance of incorporating skin-specific measures such as the Cutaneous Disease Area and Severity Index (CDASI) and the novel composite measure, Dermatomyositis Outcomes for Muscle and Skin (DMOMS). These measures provide a more balanced assessment of disease activity. Clinical trial data analyzed using these measures have demonstrated significant benefits for patients with both classic and amyopathic DM, emphasizing the need for their broader adoption.

Summary
Advancements in outcome measures are crucial for inclusive and effective myositis clinical trials. Incorporating comprehensive tools like the DMOMS can enhance the assessment of both muscle and skin disease activities, potentially leading to better therapeutic strategies and improved patient outcomes. This shift is essential for addressing the needs of all Idiopathic inflammatory myopathy patients, including those with skin-predominant DM.

Keywords
clinical outcome measures, cutaneous dermatomyositis disease area and severity index, dermatomyositis outcomes for muscle and skin, patient-reported outcomes, total improvement score

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases primarily characterized by muscle inflammation, however they also cause inflammation of other organs such as the skin, lungs, and joints. IIMs can be divided into subtypes, namely dermatomyositis (DM), polymyositis (PM), juvenile DM (JDM), antisynthetase syndrome (ASSD), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM) [1]. These diseases can present with overlapping extramuscular manifestations and nonspecific symptoms such as fever, fatigue, and arthralgias, making diagnosis challenging [2,3]. Traditionally, the 1975 Bohan and Peter criteria have been used to diagnose IIMs and are still used by some today; however, these criteria necessitate muscle involvement to qualify for diagnosis and do not delineate specific skin or exclusion criteria [4,5].

The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed and validated new classification criteria for IIM which includes the distinct pathognomonic cutaneous findings of Gottron's papules, heliotrope rash, and Gottron's sign, allowing for the diagnosis

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Curr Opin Rheumatol 2024, 36:430–437

DOI:10.1097/BOR.0000000000001044

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KEY POINTS

- Existing outcome measures for Idiopathic inflammatory myopathy (IIM) focus primarily on muscle involvement, overlooking a specific measure of skin activity or severity, particularly in cutaneous-predominant dermatomyositis (DM) patients.
- The development of composite outcome measures like Dermatomyositis Outcomes for Muscle and Skin (DMOMS) addresses the need for comprehensive assessment, enhancing trial efficacy and inclusivity.
- Clinical trials often exclude amyopathic DM patients, hindering drug development and treatment accessibility for this significant subgroup.
- Refinement of classification criteria and adoption of comprehensive outcome measures hold promise for improving research and treatment strategies for all individuals with IIM.

of DM without muscle involvement [6]. These criteria have improved the specificity and sensitivity of IIM diagnoses and have been validated by numerous studies [7–10]. However, recent clinical trials have still opted to use the Bohan and Peter criteria for patient enrollment, consequently limiting the scope of patients who can participate and in turn qualify for therapies [11]. Clinically amyopathic DM (CADM) is a subset of DM patients without muscle involvement and represents roughly 20% of all DM diagnoses [12]. Per the Bohan and Peter criteria, CADM patients do not qualify for DM diagnosis, but per the EULAR/ACR criteria, around 73.7% of CADM patients are accurately classified [13]. In an era of intense research and promising drug development for myositis, we must find a way to ensure that all patients suffering from IIM can benefit from advancements in the field by carefully considering trial design, specifically outcome measures.

Challenges in assessing disease activity in muscle

The International Myositis Assessment and Clinical Studies Group (IMACS) has comprised a list of specific myositis outcome measures that are recommended for use in clinical trials to assess changes in disease activity. These measures are also known as "core set measures" (CSMs), and include the Manual Muscle Test-8 (MMT-8), a measure of strength in eight muscles tested bilaterally (lower scores indicate weaker muscles), physician's global assessment (PhGA) of disease activity (0 represents no evidence of disease activity and 10 is extremely active or severe disease activity), patient's global assessment (PtGA) of disease activity (assessed on the same scale as used for the PhGA of disease activity); the Health Assessment Questionnaire (HAQ, in which total scores range in increments of 0.125 from 0 [no disability] to 3 [complete disability]), Extramuscular activity (higher scores reflecting more disease activity in the extramuscular organs affected by myositis), and serum muscle-enzyme levels (creatine kinase, alanine and aspartate aminotransferase, lactate dehydrogenase, and aldolase). Despite the emphasis on muscle involvement for almost all IIM outcome measures, there are many shortcomings in terms of applicability to patients. For instance, muscle enzymes are typically tracked as a marker of disease activity and are included in many outcome measures, however enzyme levels are insensitive and not always increased in IIM, especially early in the disease course [14,15,16▪]. The MMT has been classically used to assess IIM muscle involvement, but muscles damage from scarring and fibrosis could negatively impact scores and not accurately represent current disease activity. The MMT is also insensitive to changes in muscle strength and endurance, the latter of which can be a hallmark of IIM, particularly in cases where patients have high baseline strength or only minimal muscle weakness [17]. In addition, MMT results are influenced by patient effort, which can be quite variable. The Myositis Functional Index-2 (FI-2) is another assessment that seeks to quantify muscle endurance for individual muscle groups and has been shown to capture other aspects of muscle function that are not well represented by the MMT. An updated version of the FI-2, namely the FI-3, was developed to further streamline the FI-2. However, because each muscle strength task of the FI-2 and FI-3 has been validated individually, only 1 or 2 muscles group can be assessed in a trial at once [18].

Most recently in 2016 the EULAR/ACR approved the "Total Improvement Score" (TIS), a composite number representing a combination of CSMs. The individual CSMs of the TIS include the PhGA, PtGa/PhGa, MMT, HAQ, serum muscle enzyme level, and extramuscular global assessment (EMGA). These CSMs are weighted differently in terms of importance in defining change in disease activity to create the composite TIS score on a scale from 0 to 100, weighting muscle symptoms more heavily [19]. Additionally, these CSMs each have their own weaknesses. For example, the HAQ is dependent on patient compliance, and it also has a significant floor effect, whereby patients with some disability can still have a normal HAQ score. The EMGA serves to be representative of extra-muscular findings, grouping together disease activity in the skin, joints, and lungs. As a result, the TIS only indirectly

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measures cutaneous disease activity [20]. Due to the frequent use of the TIS for clinical trials, trials are continuing to move towards only including classic DM or PM patients in their studies, excluding CADM patients. Consequently, patients with skin-predominant DM face the possibility of exclusion from the officially indicated population for new medications. This exclusion can lead to challenges in obtaining insurance approval for treatments and qualifying for clinical trials, particularly when they are refractory to other treatments.

An example of this is the ProDERM trial that was a prospective, phase 3, double-blind, parallel-group, randomized, placebo-controlled trial that enrolled patients with dermatomyositis from 36 different centers. The TIS was used as the primary outcome measure. Patients were eligible for enrollment if they had muscle weakness, as determined by a score of <142 on the MMT-8, and at least two abnormal findings in the other five core measures (a score of ≥ 2 on the PhGA or PtGA of disease activity or the extramuscular disease-activity measure; an HAQ total score of ≥ 0.25; or a muscle-enzyme level >1.5 times the upper limit of the normal range) [11]. Consequently, patients with CADM did not qualify for the trial due the lack of muscle weakness and an indirect measure of cutaneous disease using the EMGA. Additionally, extramuscular disease activity was assessed using the visual analogue score (VAS), a component of the MDAAT [11], which can be a subjective and unreliable measure. Because there are no defined anchor points, the interpretation of disease activity status can vary depending on the rater and may be influenced by the VAS interpretation assigned at the previous visit.

Challenges in assessing disease activity in skin

Skin disease is a defining characteristic of DM that causes severe symptoms and should be directly measured as such in a primary endpoint. It has previously been demonstrated that cutaneous disease activity of DM significantly affects quality of life (QoL) and is refractory to standard-of-care treatments in 80% of amyopathic DM patients [21–25]. Individuals with skin-predominant DM experience debilitating pruritis, disfiguring skin disease, photosensitivity, and emotional distress due to the cutaneous disease manifestations.

The Cutaneous Dermatomyositis Disease Activity and Severity Index (CDASI) was created in 2008 and updated in 2010 due to the need to develop an outcome measure that evaluates skin disease severity for dermatomyositis patients [26,27]. Prior to this, measures such as the DAS, Cutaneous Assessment Tool (CAT) and Myositis Disease Activity Assessment Tool (MDAAT) were used. The MDAAT can be incorporated as a secondary outcome into clinical trials to measure multiple organs including skin disease activity [28]. However, these measurements have several limitations. For example, the CAT requires complete resolution of activity to show improvement, and the MDAAT assesses multiple organ systems simultaneously. All of these measures are less detailed and less sensitive than the CDASI. Consequently, although the DAS, CAT, and MDAAT have been validated and used in the JDM population, their moderate response to clinical change has led many pediatric rheumatologists to adopt the CDASI instead.

The CDASI produces a numerical score in order to stratify the overall disease status, and it consists of three activity categories of damage, erythema, and erosion/ulceration, (CDASI-A) and two damage categories of poikiloderma (dyspigmentation or telangiectasia) and calcinosis (CDASI-D). It has been validated multiple times in terms of reproducibility, sensitivity to clinical changes, and intra- and inter-rater reliability, in juvenile and adult populations, and has been used in translational and clinical studies across many medical specialties [26,29–31]. Interestingly, CDASI activity scores have also been correlated with an increase in serum interferon (IFN-β) and type 1 IFN gene signature in nearly all DM patients with moderate to severe disease activity enrolled in a prospective study [32]. This finding is significant because the type 1 IFN pathway is heavily implicated in the pathogenesis of DM and is elevated in the blood, muscle, and skin of DM patients [33].

In the Open-Label Extension period of the aforementioned ProDERM clinical trial, cutaneous disease was assessed using the CDASI. At week 16, the mean change in CDASI-A from baseline in the IVIG arm was −9.36 [95% confidence interval (CI): −12.52, −6.19] and −1.16 (−3.32, 0.99) in the placebo arm ($P < 0.0001$). These results demonstrate IVIG not only improves muscle disease but also significantly improves skin disease. ProDERM is the first large prospective, randomized trial to show the efficacy of IVIG for cutaneous manifestations of DM through improvement in the CDASI scores as a secondary endpoint [28]. Nevertheless, because the 2021 Food and Drug Administration approved IVIG for treatment of DM based on results from this trial, patients with skin-predominant DM are not explicitly included as an indicated population in the package insert and thus experience difficulty obtaining insurance coverage for IVIG therapy [34]. More recent clinical trials for DM have used the CDASI as a secondary endpoint, but with increasing

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awareness of the importance to accurately capture skin disease activity, we hope that more skin-focused measures like the CDASI will be approved as a primary endpoint.

Several myositis organizations such as the IMACS group have recommended using Patient-reported Outcome Measures (PROMs) in studies to better understand patient-prioritized symptoms and the impact of IIM on their QoL [35]. As part of this effort, numerous clinical trials have incorporated QoL measures such as the Patient Reported outcome Information System (PROMIS) instruments, which have demonstrated strong validity and reliability in IIM cohorts for measuring their pain interference, fatigue, and physical functioning [36▪].

The Short Form 36 (SF-36) is another valid and reliable global medical QoL study instrument that has been used in trials for patients with DM and has been found to correlate with the CDASI. It includes 36 items with 2–6 response options, scored from 0 to 100 (0 = maximum disability). The scores are divided into eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. They are subsequently added to create physical and mental composite scores [24]. Although this helps to better understand the patient's health-related QoL, there are no skin-specific questions.

To address the need for skin-specific quality of life measures, the Skindex-29 has been validated as a measure of QoL based on how skin disease affects functioning, emotions, and symptoms, and is used in clinical trials. One study sought to correlate the minimal clinically important difference (MCID), or the subjective meaningful change from the patient's perspective, for both the Skindex-29 and the Dermatology Life Quality Index (another validated QoL) to a change in CDASI scores. A meaningful change in QoL correlated with a 40% improvement in CDASI scores from baseline (defined in this study by a CDASI score greater than 14), which is helpful for future clinical trials in assessing meaningful changes in QoL [37]. More specifically, a MCID correlated with a 7- and 10-point increase in the Skindex-29 categories of symptoms and emotions, respectively. Furthermore, Dan *et al.* demonstrated an increase of 8 points on the CDASI scale is correlated with a clinically significant cutaneous flare and worsening QoL [38].

Similar to the Skindex-29, the Skindex-16 measures the impact of the skin diseases on patient's QoL using the same breakdown of functioning, emotions, and symptoms [39]. In a study comparing the two outcome measures in DM patients, both were deemed viable and produced equivalent responses, therefore suggesting that the Skindex-16 may be used instead of the 29 to reduce response burden [40▪]. The Skindex-29+3, an extension of the Skindex-29, integrates three targeted questions addressing hair loss and photosensitivity. Originally validated for patients with cutaneous lupus erythematosus, a recent study applied the Skindex-29+3 to DM populations. This study showed a notable impact of photosensitivity on the QoL of DM patients, and also highlighted widespread concern among patients regarding hair loss [39,41▪].

PAVING THE WAY FORWARD

The dermatomyositis outcomes for muscle and skin (DMOMS) is a new composite outcome measure that includes components of the TIS; however, unique to DMOMS, it includes skin outcome measures that specifically measure change in cutaneous disease (Table 1). The DMOMS includes the MMT, PGA, and PtGA with a 50% increase in the weight of the PtGA as well as the CDASI weighted equally to the MMT score [42]. This development addresses the gap in clinical trials that have primarily focused on muscle weakness, despite the significant number of patients with recalcitrant amyopathic DM.

The lenabasum DM trial highlights the significant impact of outcome measures in clinical research. Lenabasum is a cannabinoid receptor type 2 agonist that modulates inflammatory and immune responses and underwent a phase 2 and phase 3 clinical trials for DM patients. In the phase 2 trial, the disease activity decreased more for those randomized to the treatment group starting on day 43, and by day 113, this difference was significant. There were no serious or severe adverse events and no study discontinuation due to lenabasum. This is significant considering that alternative treatments for DM, like immunosuppressants, have more side effects and complications. Those randomized to the lenabasum arm also showed greater improvement in physician-reported and patient-reported VAS scores of overall disease activity, patient-reported VAS scores for global skin disease and pain, Skindex-29 symptoms score, concern about hair loss, and Patient-Reported Outcomes Measurement Information System-29 physical function and pain interference domains [43▪]. It is important to note that extramuscular disease activity was assessed using the VAS of the MDAAT, which can be a subjective and unreliable measure. Because there are no defined anchor points, the interpretation of disease activity status can vary depending on the rater and may be influenced by the VAS interpretation assigned at the previous visit.

Unfortunately, the phase 3 lenabasum trial for DM patients failed to meet the primary outcomes

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Table 1. Comparison of the DMOMs and TIS outcome measures for dermatomyositis

Core set measure	Total Improvement Score (TIS) levels of improvement	Individual TIS CSM % weight of maximum score, improvement scale	Dermatomyositis Outcomes for Muscle and Skin (DMOMS) levels of improvement	Individual DMOMS CSM % weight of maximum score, improvement scale
Patient Global Activity (PtGA)	Worsening to 5% improvement >5% to 15% improvement >15% to 25% improvement >25% to 40% improvement >40% improvement	10% 0–2.5–5–7.5–10	≤ 0.5 point improvement 0.6–1.5 point improvement 1.6–2.5 point improvement 2.6–4.0 point improvement ≥ 4.1 point improvement	15% 0–4–7.5–11–15
Physician Global Activity	Same as PtGA scale	20% 0–7.5–15–17.5–20	Same as PtGA scale	20% 0–7.5–15–17.5–20
Manual Muscle Testing (MMT)	Worsening to 2% improvement >2% to 10% improvement >10% to 20% improvement >20% to 30% improvement >30% improvement	32.5% 0–10–20–27.5–32.5	≤ 3 point improvement 4–7 point improvement 8–12 point improvement 13–19 point improvement ≥ 20 point improvement	32.5% 0–10–20–27.5–32.5
CDASI-A score	-	-	Same as MMT scale	32.5% 0–10–20–27.5–32.5
Extramuscular Activity (EGMA)	Same as PtGA scale	20% 0–7.5–15–17.5–20		-
Enzymes (most abnormal)	Same as PtGA scale	7.5% 0–2.5–5–7.5–7.5		-
Health Assessment Questionnaire	Same as PtGA scale	10% 0–2.5–5–7.5–10		-

because the muscle patients did not improve. However, 10% of the patients had CADM and analysis of data from the phase 3 lenabasum trial in CADM patients revealed that improvements in the CDASI score corresponded with the degree of patient- or physician-reported skin disease improvement, consistently reflecting clinical progress between weeks 16 and 52. The percentage of patients in the treatment arm that responded with at least minimal improvement was significantly greater than those in the placebo arm. The CDASI-A proved to be the most sensitive outcome measure for patient- and physician-reported improvement in cutaneous disease, surpassing the efficacy of the TIS in capturing change (Figs. 1 and 2) [44]. Other clinical trials, including the ProDERM trial, have also demonstrated a robust longitudinal correlation between CDASI-A scores and changes in patient-reported outcomes [28,45,46]. To further understand how skin activity affects quality of life in DM trials, it is imperative to incorporate both the CDASI-A and skin-specific QoL measures into clinical trials. This approach will broaden our data collection efforts, providing more robust measures to assess changes in patients with skin-predominant DM.

Currently, trials tend to exclude amyopathic DM patients, and recruiting participants proves challenging due to insufficient numbers of individuals exhibiting the requisite level of weakness. Moreover, in cases where patients are exceptionally weak, clinicians may hesitate to randomize patients to a trial where the placebo arm requires no change in treatment for up to a year, fearing potential exacerbation of their condition.

Nevertheless, these obstacles can be addressed in two ways. First, to provide validated skin criteria that can be used as a predominant means to classify DM patients. A group of rheumatologic dermatologists recently created a more inclusive criterion to benefit skin-predominant DM patients through rigorous statistical analysis, and this data is set to undergo forward validation and adjustment [47▪]. Second, with the validation of new and improved criteria comes the opportunity for new outcome measures that equally weigh and value skin symptoms in conjunction with muscle symptoms, such as DMOMS. Data from the phase 3 lenabasum trial was analyzed for efficacy of the TIS versus DMOMS scores in assessing skin and muscle disease involvement. When compared to the TIS, DMOMS showed twice the treatment effect for responders versus nonresponders in muscle and skin improvement, without any increase in score in nonresponders [42]. Therefore, DMOMS is a more sensitive indicator of baseline improvement in DM and may be more effective for assessing muscle and skin treatment effects in future clinical trials for DM. While DMOMS stands out among current measurements, the ongoing development of additional sensitive

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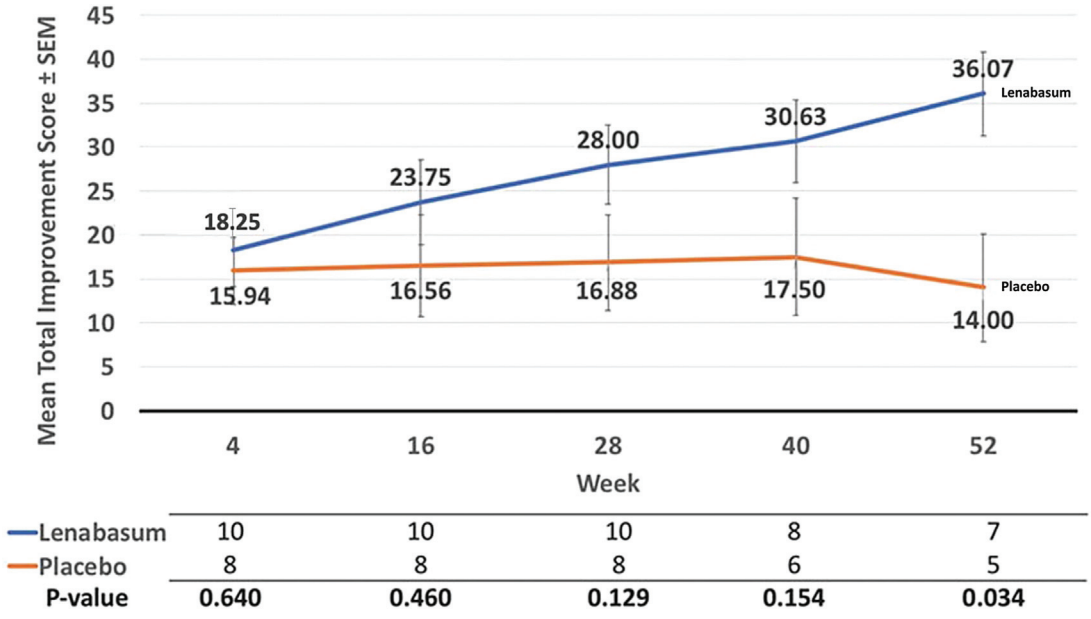

FIGURE 1. Results from the DeterMine trial using the Total Improvement Score. Mean Total Improvement Score (TIS) over 52 weeks for dermatomyositis (DM) patients treated with lenabasum 20 mg b.i.d. and placebo. Error bars represent the standard error of the mean (SEM). The study was stopped after all subjects completed Week 28, with some subjects having completed Week 52. *P*-values indicate no significant differences between the groups at each time point.

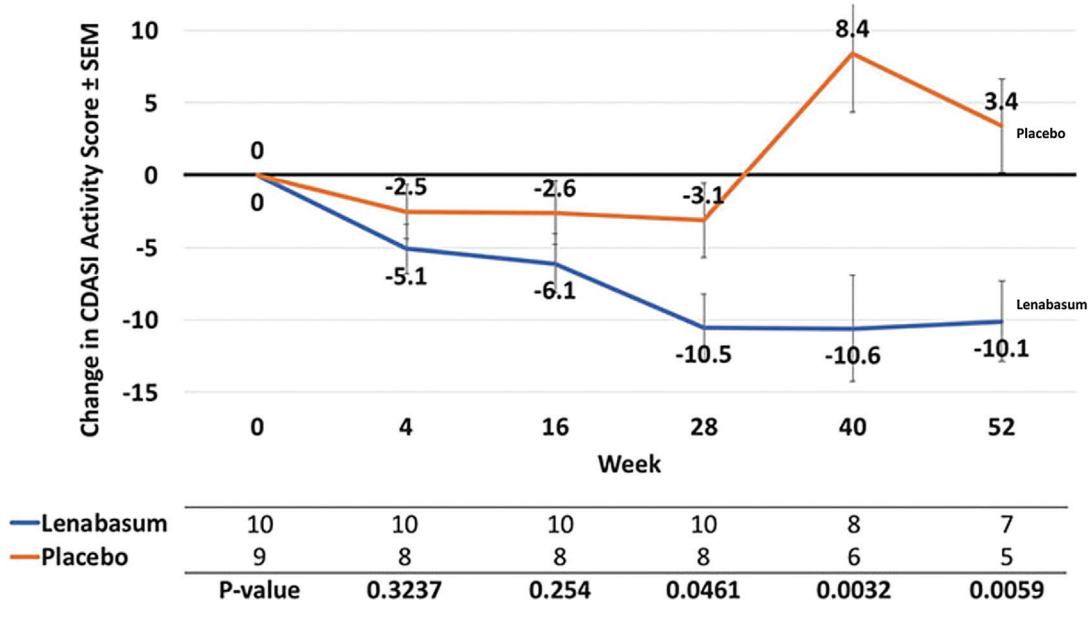

FIGURE 2. Results from the DeterMine trial using the Change in Cutaneous Dermatomyositis Disease Area and Severity Index. Change in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score over 52 weeks for DM patients treated with lenabasum 20 mg BID and placebo. Error bars represent the standard error of the mean (SEM). The study was stopped after all subjects completed Week 28, with some subjects having completed Week 52. *P*-values indicate statistical significance at Weeks 28 ($P = 0.0461$) and 52 ($P = 0.0059$) for lenabasum compared to placebo.

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measures for muscle and skin assessment holds promise for further refining evaluation methodologies.

CONCLUSION

In conclusion, the management of DM, particularly its cutaneous manifestations, presents a significant challenge due to the limited focus of clinical trials and the inadequacy of existing outcome measures to capture the full spectrum of the disease. With skin-predominant DM patients constituting a substantial portion of those affected, it is imperative to broaden the scope of research and treatment strategies to address their unique needs. The ProDERM trial and the lenabasum studies underscore the potential efficacy of interventions targeting cutaneous symptoms, yet hurdles remain in obtaining approval and coverage for these treatments. Moving forward, the refinement of classification criteria for DM, such as the ongoing efforts to develop new criteria, along with the adoption of comprehensive outcome measures like the DMOMS and CDASI, hold promise in ensuring inclusivity and efficacy in future clinical trials. By prioritizing the holistic assessment of both skin and muscle involvement, we can find more effective therapies and improved outcomes for all individuals living with IIM, regardless of their clinical phenotype.

Acknowledgements

None.

Financial support and sponsorship

This manuscript was funded by the National Institutes of Health-USA (NIH-USA) grants R01AR071653 (to V.P. Werth), and the United States Department of Veterans Affairs Merit Review BX005921-01 (Veterans Health Administration, Office of Research and Development and Biomedical Laboratory Research and Development, to V.P. Werth).

Conflicts of interest

V.P. Werth has grants from Pfizer, Biogen, Gilead, Corbus Pharmaceuticals, Viela, Amgen, Regeneron, Argenx, CSL Behring, Ventus, q32 Bio, BMS, Horizon Priovant Pharmaceuticals, and has consulted for Genentech, Janssen, Lilly, Pfizer, Biogen, BMS, Gilead, Amgen, Medscape, Nektar, Incyte, EMD Sorona, CSL Behring, Principia, Crisalis, Viela Bio, Argenx, Kwoya Kirin, Regeneron, Principia, AstraZeneca, Abbvie, Octapharma, GSK, Astra-Zeneca, Cugene, UCB, Corcept, Beacon Bioscience, Rome Pharmaceuticals, Horizon, Gilead, Merck, Kezar, Sanofi, Bayer, Akari, Calyx, Cabaletta Bio. The University of Pennsylvania owns the copyright for the CDASI and DMOMS.
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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This newly proposed classification criteria will include skin-predominant DM patients.

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