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INFLAMMATORY MUSCLE DISEASE (I LUNDBERG AND L DIEDERICHSEN, SECTION EDITORS)

Recent Advances in Pharmacological Treatments of Adult Dermatomyositis

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Abstract

Purpose of the Review Dermatomyositis (DM) is an uncommon autoimmune disease that primarily affects the skin, muscle, and/or lungs, and remains a therapeutic challenge. We discuss recent studies evaluating efficacy of conventional treatments for clinically amyopathic DM (CADM), DM-associated interstitial lung (ILD) disease, and classic DM (CDM). We highlight several emerging new therapies with a focus on clinical trials, systematic reviews, and case series in the last 5 years.

Recent Findings Recent studies report a significant number of patients remain refractory to antimalarials and require second- and third-line agents. Effective treatment for DM-associated ILD can vary based on patient specific antibodies. CDM requires oral glucocorticoids; recent studies have evaluated the benefits of adjunctive therapies including methotrexate and calcineurin inhibitors. New therapies target cell populations or cytokines thought to drive disease pathogenesis.

Summary Dermatomyositis is an autoimmune disease that remains challenging to treat. Many patients are refractory to conventional therapies, warranting the development and evaluation of new treatments.

Keywords Clinically amyopathic dermatomyositis · Classic dermatomyositis · Interstitial lung disease · Therapeutics · Treatment algorithms

Introduction

Dermatomyositis (DM) is an autoimmune disease that can affect the skin, muscles, and/or lungs, among other organs. Skin findings include heliotrope rash, shawl sign, and Gottron's sign/papules [1]. Muscle findings include symmetric proximal weakness, elevated serum muscle enzymes, and abnormalities on electromyography (EMG) and muscle biopsy [1]. DM can be classified as either classic DM (CDM) or clinically amyopathic DM (CADM), distinguished by the absence of clinical evidence of myositis for 6 months in the absence of steroids or immunosuppressives for more than 2 months in CADM [2]. The incidence of CDM and CADM is estimated to be 9.63 per 1 million persons and 2.08 per 1 million persons, respectively [3]. Both CDM and CADM can be associated with interstitial lung disease and rapidly progressive interstitial lung disease [4], emphasizing the necessity of recognizing and treating disease early on.

Because DM is uncommon, clinically heterogeneous, and frequently recalcitrant to conventional treatments, it remains a therapeutic challenge. CADM is commonly treated with antimalarials, steroid-sparing immunosuppressives, and/or IV immunoglobulin (IVIg) [5••]. CDM is conventionally treated more aggressively early on with corticosteroids alone or in combination with immunosuppressive, steroid-sparing agents [6]. Despite their empiric use, evidence for these conventional therapies is limited and only recently emerging. At the same time, several biologicals are being trialed, some of which have shown promising results in case series, open-label studies, and/or randomized controlled trials. This review article will focus on clinical trials, systematic reviews, and case series within the last 5 years pertaining to both conventional and biological treatments for CADM, DM-associated ILD, and CDM.

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Pathogenesis

The pathogenesis of DM remains incompletely understood. It is thought that predisposing genes, environmental stressors, and immune- and non-immune-mediated mechanisms induce susceptibility and onset of DM [7••]. In DM skin, the predominating infiltrating cells are CD4+ cells, dendritic cells, and mast cells [8]; in DM muscle and lung, B cells are additionally found in high densities [9]. It is thought this inflammation causes injury to adjacent keratinocytes in skin as well as adjacent parenchyma and blood vessels of muscle [10]. Cytokines, particularly interferon (IFNs), appear to play an important role in disease pathogenesis as an IFN signature characterizes both DM skin and muscle [11]. Additionally, IFN-β and IFN-γ transcripts correlate with the IFN signature in DM skin [11]. IFNs contribute to maturing dendritic cells, activating T cells and disrupting tolerance to self-antigens; they may additionally directly induce vascular damage and apoptosis [9]. Better understanding of DM pathogenesis will certainly permit development of more targeted therapies.

Treatment Guidelines

The American Academy of Dermatology (AAD) Guidelines and Outcomes Committee published a treatment guideline for DM in 1996 (Table 1) [12]. However, in the USA, there is no consensus on the first-line treatment for CADM or whether treatment should differ from CDM [13••]. Furthermore, while the medications from the AAD guidelines are commonly used in CADM, up until recently, there were no randomized controlled trials or robust observational studies evaluating the efficacy of these treatments [13••]. In 2016, the German Society of Neurology published guidelines on dermatomyositis as part of the larger interdisciplinary S2k guidelines on diagnosis and therapy of myositis syndromes (Table 1) [14••]. In Japan, a research team of rheumatologists, neurologists, and dermatologists agreed upon a multidisciplinary treatment algorithm for the management of DM which was approved by the Japan College of Rheumatology, Japanese Society of Neurology, and Japanese Dermatologic Association; their treatment algorithm was published just this year (Table 1) [15••].

Clinically Amyopathic Dermatomyositis

In cases of mild CADM, topical corticosteroids and calcineurin inhibitors are used to manage cutaneous inflammation and pruritus. For more severe disease, antimalarials are considered first-line therapy but frequently require second-line cytotoxic agents; in severely refractory cases, IV immunoglobulin (IVIg) and/or systemic calcineurin inhibitors may be employed.

Despite empiric acceptance within the dermatologic community, systematic evaluation of these therapies is relatively recent. In 2017, Anyanwu and colleagues reported that among 41 patients with CADM at a single center, 56.1% of patients received antimalarial medication alone, whereas 43.9% required second- and third-line therapies [16]. Only 24.4% of patients were adequately treated with hydroxychloroquine (HCQ) alone, many often requiring a switch to chloroquine (CQ) and/or addition of quinacrine (Q) [16]. The authors concluded that patients with CADM often require second-line therapies as antimalarial medications are frequently insufficient for adequate disease control [16].

Most recently, a study evaluating 115 CADM patients from 4 tertiary care centers found 76.5% were treated with antimalarials, but only 11.4% of those patients achieved adequate control of skin disease [5••]. In fact, 80.0% of patients required at least one immunosuppressive agent and a median of three medications to achieve skin disease control [5••]. The most common non-antimalarials used were methotrexate (MTX) (used in 51.3% of patients), mycophenolate mofetil (MMF) or mycophenolic acid (used in 40.0% of patients), and IVIg (used in 28.7% of patients) [5••]. This study again underscored that although antimalarials are typically considered first-line therapy for cutaneous DM, it is rarely adequate to control disease activity. A systematic review of 153 patients found that while antimalarials were most commonly used for CADM, 55% of patients discontinued these treatments due to lack of improvement or failure to wean concomitant steroids [13]. Additionally, 60% of patients tried more than one treatment due to side effects or lack of efficacy, again highlighting the need for more effective therapies [13].

In some patients with refractory cutaneous DM, IVIg has been shown to be safe and efficacious for the treatment of skin disease [17•]. In a retrospective review of 42 patients, 83% showed improvement in cutaneous DM after an average of 1.82 ± 1.38 IVIg cycles, allowing for decrease or discontinuation of systemic glucocorticoids and/or immunosuppressives in 80% of patients [17•]. Another retrospective study of 27 DM patients reported significant cutaneous improvement in 70% of patients who had previously failed photoprotection and at least one medication [18]. These patients required a mean of 4.8 IVIg cycles to achieve adequate control [18]. Of note, 63% of the patients received concomitant therapy. Although 53% of patients relapsed after approximately 6 months following their last course of IVIg, one additional course of IVIg was sufficient to successfully control disease [18].

Table 1 Treatment Guidelines

AAD Guidelines for Care of Dermatomyositis	
General	• Rest • Adequate nutrition • Physical therapy
Skin Disease	• Photoprotection • Aminoquinolone antimalarials • Oral systemic steroids • Steroid-sparing immunosuppressives (methotrexate, azathioprine, cyclosporine)
Muscle Disease	• Oral systemic steroids • Steroid-sparing immunosuppressives (methotrexate, azathioprine, cyclophosphamide) • IVIg • Total body irradiation • Plasmapheresis
German Society of Neurology Guideline on Dermatomyositis	
Skin Disease	• Photoprotection • Topical corticosteroids ± calcineurin inhibitors • Systemic treatment (antimalarials, methotrexate, corticosteroids) • IVIg • Rituximab
Muscle Disease	• Oral systemic steroids • Steroid sparing immunosuppressives • IVIg
Japanese Multidisciplinary Treatment Consensus of Dermatomyositis	
Skin-only Disease	• Photoprotection and topical corticosteroids • Systemic treatments in severe cases
Interstitial Lung Disease	• High-dose corticosteroids and immunosuppressants
Skin and Muscle Disease	• High-dose glucocorticoids OR • Intermediate-dose glucocorticoids and immunosuppressants

DM-Associated Interstitial Lung Disease

DM is commonly associated with both interstitial lung disease (ILD) and rapidly progressive interstitial lung disease (RP-ILD), and is a prognostic factor for poor outcome requiring early and effective treatment. Anti-melanoma differentiation associated gene-5 (MDA-5) and anti-aminoacyl-tRNA synthetase (ARS) antibodies are the two myositis-specific antibodies most strongly associated with ILD [19]. Anti-MDA-5 is more commonly associated with CADM and RP-ILD, particularly in East Asians, whereas anti-ARS antibodies are associated with CDM/CADM and chronic progressive ILD (C-ILD) [19]. Treatment regimens vary depending on which antibodies are present and their predicted clinical course.

Anti-MDA-5-associated ILD responds best to combination therapy of oral corticosteroids, IV cyclophosphamide, and calcineurin inhibitors [19]. MMF has also been recommended as the initial corticosteroid sparing agent as it has shown efficacy in case series and appears to attenuate the progression of lung disease by reducing profibrotic cytokines [20, 21]. In contrast to anti-MDA-5-associated ILD, which does not respond well to corticosteroid monotherapy, anti-ARS-associated ILD responds more favorably, as least in the short term [19]. These patients may experience progression or recurrence of ILD and therefore may eventually benefit from concomitant calcineurin inhibitors or rituximab [19]. While calcineurin inhibitors seem to improve progression-free survival when used in conjunction with corticosteroid monotherapy [22, 23], there is no difference in long-term survival between those on corticosteroid monotherapy and those on both corticosteroids and calcineurin inhibitors [22].

More broadly, in a systematic review and meta-analysis including 27 studies and 553 patients, Barba and colleagues assessed the efficacy of therapies used for RP-ILD and C-ILD in patients with idiopathic inflammatory myopathies (IIM), including those with DM [24••]. Survival rates at 3 months for RP-ILD were 51.7% for corticosteroids alone, 69.2% for cyclosporine (CsA), and 72.4% for cyclophosphamide [24]. Another study found early treatment with CsA significantly improved survival compared with delayed treatment in DM-associated RP-ILD [25]. In C-ILD, functional improvement rates were 89.2% for corticosteroids alone, 80.7% for CsA, 64.1% for azathioprine (AZA), 86.2% for tacrolimus, 56.4% for cyclophosphamide, and 76.6% for rituximab [24].

Classic Dermatomyositis

First-line treatment for CDM is oral glucocorticoids; however, because there are few randomized, placebo-controlled clinical

trials, there is no consensus regarding dosing, length of treatment, tapering speed, or when to add which immunosuppressant in steroid resistant disease [26]. Retrospective studies have suggested that the greatest improvement in DM occurs with aggressive steroid treatment within the first 6 to 12 months, which remains stable for at least 36 months following disease control and permits steroid tapering and potential discontinuation [26, 27]. Despite this, corticosteroid sparing agents including MTX, AZA, and MMF are frequently utilized, as corticosteroid monotherapy is often insufficient. In a retrospective study of 108 patients with inflammatory myopathies, including 57 with CDM and 9 with amyopathic DM, only 14% were stable with exclusively corticosteroid monotherapy [28].

A randomized, open-label trial in adult DM and polymyositis (PM) assessing the efficacy and safety of MTX plus prednisone versus prednisone alone is ongoing (NCT00651040). Results of this trial will be pivotal in ultimately agreeing upon an efficacious treatment regimen, as we are currently limited to retrospective studies and case series. In juvenile DM (JDM), a robust, randomized study evaluated the efficacy and safety of prednisolone alone versus prednisolone plus either MTX or CsA in 139 pediatric patients from 54 centers in 22 countries [29••]. They concluded that combined therapy with prednisolone with either CsA or MTX is more effective than prednisolone alone; however, MTX is more favorable than CsA from a safety profile standpoint [29].

Tacrolimus (TAC), a calcineurin inhibitor, is another drug that appears to be efficacious when used in conjunction with corticosteroids in refractory disease. One systematic review evaluated 8 studies and 134 patients for outcomes and side effects in patients who received either TAC alone or in conjunction with glucocorticoids for the treatment of DM or PM [30]. They found TAC improves muscle strength and lung function in the majority of patients and permitted reduction of glucocorticoid doses to approximately one-third of the original dose [30]. Side effects were minimal but included nephrotoxicity, hypomagnesemia, tremors, and hypertension [30]. A subsequent retrospective study similarly investigated the therapeutic advantage of treating DM and PM patients with prednisolone and tacrolimus or tacrolimus alone for skin and muscle disease [31]. They found that concomitant TAC significantly lowered relapse frequency and increased remission periods compared with patients treated with prednisolone alone [31]. A similar retrospective study including 19 DM/PM patients without severe ILD found hospitalization periods were significantly shorter with TAC plus prednisolone combination therapy and permitted the reduction of corticosteroid doses [32].

Emerging Therapeutics

Given the number of patients who remain refractory to conventional treatment or require long-term glucocorticoids, new therapeutics are necessitated for CADM, DM-ILD, and CDM. Many of these are biologics targeting specific cell types, pathways, or cytokines thought to be driving disease pathogenesis (Table 2). They have been studied in the skin, muscle, and/or lungs to varying degrees.

Therapies Targeting Cell Populations

Rituximab—Anti-CD20 Antibody

Rituximab (RTX) is a chimeric monoclonal antibody against the CD20 antigen protein on B cells. Depletion of B cells with RTX affects cytokine release, antibody production, and antigen presentation to T cells [33]. Results of several studies have generally been promising for muscle disease although there are mixed reports for its effect on skin disease.

One of the earliest studies looking at RTX in DM was an open-label pilot trial involving 8 adult patients at Stanford University [33]. They reported limited effects on skin and modest effects on muscle disease, as measured by the Dermatomyositis Skin Severity Index and Manual Muscle Test, respectively, at 6 months [33]. More recently, in a randomized placebo-phase-controlled trial, 72 adult DM and 48 JDM patients were treated with RTX either in early or late drug arms to assess the efficacy of RTX on cutaneous manifestations [34]. Patients remained on concomitant background therapy [34]. There was significant improvement in cutaneous disease activity following the treatment in both study arms based on the Myositis Disease Activity Assessment Tool, which uses a visual analog scale (VAS), in both adult DM (VAS decrease from 3.22 to 1.72, $p = 0.0002$) and JDM (VAS decrease from 3.26 to 1.56, $p < 0.0001$) [34]. Of note, faster response was found with the earlier drug arm ($p = 0.052$) in adult DM [34]. Another study, though retrospective, examined 43 patients with IIM, including 16 with DM, and found that 75% of the 38 patients who completed the 1-year follow up attained clinical and laboratory response based on modified International Myositis Assessment & Clinical Studies Group (IMACS) core set measures [35]. Glucocorticoid dose significantly decreased from 18.8 mg/day to 6.3 mg/day and 42% of patients were able to discontinue prednisone [35]. These mixed reports may be in part attributed to the heterogeneity of the disease, and Aggarwal and colleagues have identified clinical and laboratory predictors of RTX response including antisynthetase and anti-Mi-2 autoantibodies [36].

An ongoing prospective, multicenter, randomized, double blind controlled trial, RECITAL (NCT01862926), is currently comparing RTX vs. cyclophosphamide in the treatment of connective tissue disease–associated ILD [37••]. A total of 116 subjects will be randomized, followed for 48 weeks, and assessed primarily for change in forced vital capacity at 6 months [37••]. Despite somewhat inconsistent reports

Table 2 Emerging therapies and levels of evidence

Treatment	Mechanism of Action	Author, Year	Level of Evidence
Targeting Cells			
Rituximab	Anti-CD20 antibody	De Souza et al., 2018	Retrospective study
		Aggarwal et al., 2017	Randomized controlled trial
		Saunders et al., 2017	Randomized controlled trial
		Chung et al., 2007	Open-label study
Abatacept	Anti-CTLA-4 antibody	NCT02971683	Current phase III trial
		Tjärnlund et al., 2018	Randomized delayed start trial
Targeting Cytokines			
Lenabasum	CB2 receptor agonist	NCT03813160	Current phase III trial
		NCT02466243	Current open label extension
		Werth et al., 2017	Randomized controlled trial
Tofacitinib	JAK - 1/3 inhibitor	Moghadman-Kia et al., 2019	Case series
		Paik et al., 2018	Open label study
		Alsarheed et al., 2018	Case series
		Kurasawa et al., 2018	Case series
		Kurtzman et al., 2016	Case series
Ruxolitinib	JAK - 1/2 inhibitor	Hornung et al., 2014	Case report
Infliximab	TNF-α inhibitor	Schiffenbauer et al., 2018	Randomized controlled trial
Apremilast	PDE-4 inhibitor	NCT03529955	Current phase II trial
		Bitar et al., 2018	Case report
Sifalimumab	Anti-IFN-α monoclonal antibody	Guo et al., 2014; Higgs et al., 2014	Randomized controlled trial
Anakinra	IL-1 receptor antagonist	Groh et al., 2015	Case report
		Zong et al., 2014	Open label study
Tocalizumab	IL-6 receptor antagonist	Kondo et al., 2014	Case report
		NCT02043548	Current phase II trial
Others			
Adrenocorticotropic hormone gel	Steroidogenesis, anti-inflammatory, immunomodulatory	Fernandez et al., 2018	Open label study
		Aggarwal et al., 2018	Open label study

regarding the efficacy of RTX, it seems to be beneficial in at least a subset of patients and may be considered in patients recalcitrant to conventional therapies.

Abatacept—Anti-CTLA-4 Antibody

Abatacept is a fully human fusion protein of cytotoxic T lymphocyte–associated antigen (CTLA-4) and the Fc portion of human IgG1 that has previously been successful in reducing disease activity of rheumatoid arthritis [38]. It is currently being studied in a phase III trial comparing Abatacept with standard treatment vs. standard treatment alone (NCT02971683). Results of a phase IIb delayed-start trial including 20 patients found that 2 of 9 DM patients and 6 of 11 PM patients responded to treatment as defined by the IMACS definition of improvement [39••]. The total improvement score was significantly higher with early treatment compared with delayed treatment ($p = 0.03$) at 3 months and this trend continued at 6 and 9 months [39••]. There was a significant increase ($p < 0.05$) in regulatory T cells in muscle biopsies after treatment compared with before treatment, suggesting a positive effect of treatment in muscle tissue [39••]. Adverse effects were mild to moderate in nature and most commonly involved infection of the upper respiratory tract or cardiovascular effects [39••].

Therapies Targeting Cytokines

Lenabasum

Lenabasum is a synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 (CB2R) agonist that has been shown to suppress TNF-α, IFN-α, IFN-β production from peripheral blood mononuclear cells in DM patients [40]. It recently entered into phase III (NCT03813160) for cutaneous DM and a long-

term open label extension trial is ongoing (NCT02466243). In its phase II trial, it was shown to be efficacious and safe [41]. All subjects on Lenabasum had clinically meaningful improvement in the Cutaneous Disease Activity and Severity Index (CDASI) activity scores [41]. Additionally, it showed greater improvement than placebo in the CDASI damage index, patient-reported global skin disease, skin symptoms including photosensitivity, itch, fatigue, sleep, pain, and physical function [41]. There were no serious or unexpected adverse events related to Lenabasum and tolerability was excellent [41].

Tofacitinib – JAK - 1/3 Inhibitor

Tofacitinib, an oral Janus Kinase (JAK)-1/3 inhibitor, is another potential therapy for the treatment of recalcitrant cutaneous DM. It is currently approved for treatment of rheumatoid arthritis and has been efficacious in other inflammatory diseases including vitiligo, psoriasis, alopecia areata, and atopic dermatitis [42]. It is thought to suppress interleukin and interferon signaling, major pathways in DM pathogenesis [42].

Recently, a small study of 7 patients with recalcitrant cutaneous DM were treated with tofacitinib at either 10 mg twice daily or 5 mg twice daily [43]. All 7 experienced clinically significant cutaneous improvement, with a mean improvement of 13 points on the CDASI activity scale; 6 of 7 patients transitioned from moderate-severe cutaneous disease to mild disease [43]. Pruritus improved in all patients and no adverse effects were observed [43]. A number of case series have additionally supported the efficacy of tofacitinib in refractory cutaneous DM [42, 44, 45].

The results of an open label pilot study of tofacitinib were presented at the 2018 American College of Rheumatology (ACR) annual meeting with promising findings in muscle disease [46]. The study aimed to evaluate the efficacy and safety of tofacitinib in the treatment of 9 subjects with active, refractory DM [46]. Five of the 9 subjects achieved moderate improvement and the remaining 4 showed minimal improvement based on the Total Improvement Score of the Myositis Response Criteria and a corresponding decrease in associated chemokine levels [46].

Ruxolitinib – JAK - 1/2 Inhibitor

While no clinical trial has systematically assessed the efficacy of Ruxolitinib, a case report suggests its potential benefit in severely refractory DM [47]. Ruxolitinib, a selective JAK-1/2 inhibitor, inhibits the pathway used by type I IFNs thought to drive DM inflammation [47]. A 72-year-old woman with recalcitrant DM was previously treated with high dose glucocorticoids and azathioprine without disease control [47]. She was later started on IVIg, MMF, and prednisone which achieved partial disease control, decreasing her CDASI activity score from 30 to 12 [47]. However, following development of post-polycythemia vera myelofibrosis, she was treated with ruxolitinib, which completely resolved DM associated skin lesions and restored muscle strength and body weight [47].

Infliximab

TNF-α inhibitors have shown inconsistent results in the treatment of DM depending on the patient. There are even several reports of anti-TNF-α-induced DM [48–51]. One recent randomized, double-blind, placebo-controlled trial of infliximab including 12 subjects with active DM or PM suggested that infliximab is well tolerated and may be beneficial in a subset of patients [52]. Patients received either placebo or infliximab at 5 mg/kg doses and had the option of continuing in the same treatment arm or crossing over to the non-responder treatment arm at week 16 [52]. Of the treatment group, only 1 of 6 patients responded at the 5 mg/kg dose; 3 of the 5 remaining subjects crossed into the non-responder treatment arm and subsequently received a 7.5 mg/kg dose; 2 of those subjects responded [52]. All 6 of the subjects in the placebo group crossed into the non-responder treatment arm and 2 responded [52].

Apremilast

Apremilast is a phosphodiesterase-4 (PDE-4) inhibitor that has previously been reported in the treatment of psoriasis, psoriatic arthritis, and Behçet's disease [53]. Inhibition of PDE-4 increases the level of cyclic adenosine monophosphate (cAMP) resulting in a decrease in proinflammatory cytokines including TNF-α and IFN-γ, which are thought to be involved in disease pathogenesis [53]. In a recent case series report, apremilast was found to be effective in 3 patients with moderate to severe, recalcitrant DM [53]. On average, an 85% improvement in CDASI activity score was seen in the skin after 3 months of treatment in all patients [53]. Although improvement in muscle disease was slower, all 3 patients did have normalization of their muscle enzymes [53]. Two of 3 patients were able to discontinue all other medications and use apremilast as monotherapy [53]. This drug is currently being evaluated for efficacy, safety and toxicity in a phase II clinical trial for the treatment of cutaneous disease in patients with recalcitrant DM (NCT03529955).

Sifalimumab

Sifalimumab is an anti-IFN-α monoclonal antibody evaluated in a phase Ib randomized double-blind placebo controlled clinical trial in DM/PM patients. The effects of the drug on the type I IFN signature in DM/PM serum and muscle were studied [54]. They found sifalimumab decreased type I IFN

signature in both serum and muscle [54]. Additionally, there was a positive correlation between IFN neutralization and improvement in disease activity [54]. Neutralization of the type I IFN gene signature appears to suppress T cell related proteins including interleukin (IL)-2RA, TNFR2, and IL-18 [55]. Interestingly, however, two studies have shown that DM disease activity correlates with IFN-β, not IFN-α [11, 56••].

Anakinra – IL-1 Receptor Antagonist

Anakinra is a recombinant IL-1R antagonist that may be useful in the treatment of DM and/or CADM. In an open label trial including 15 patients with refractory myositis (4 with DM) treated with anakinra for 12 months, 3 of the 4 DM patients responded to treatment as defined by the IMACS criteria of response while 1 worsened [57]. Three of the 4 patients also showed an improvement in their cutaneous symptoms however no validated skin index was utilized to assess changes [57]. A case report noted the efficacy of anakinra in a patient with severe, refractory anti-MDA-5 CADM and suggested it may be a promising treatment for refractory CADM [58].

Tocilizumab – IL-6 Receptor Antagonist

Tocilizumab is an antagonist against the IL-6 receptor that is currently approved for rheumatoid arthritis. Given its effect on the proinflammatory cytokine IL-6, which is expressed in muscle tissue of DM, it has gained interest as a potential therapy for treatment refractory DM. In a report of a 32-year-old Japanese patient with features of both DM and systemic sclerosis, tocilizumab resulted in resolution of skin symptoms, improvement in arthritis, and gradual improvement in muscle weakness and creatine kinase elevation following poor response to high-dose prednisolone, and trials of cyclosporine, IV cyclophosphamide, IVIg, tacrolimus, methotrexate, and adalimumab [59].

The University of Pittsburgh is currently leading a phase II multi-center randomized, double-blind, controlled trial in patients with refractory adult DM and PM to study the efficacy of tocilizumab (NCT02043548).

Other Approaches

Repository Corticotropin Injection – Adrenocorticotropic hormone

Repository corticotropin injection (RCI) is a long-acting full-sequence adrenocorticotropic hormone (ACTH) and includes additional pro-opiomelanocortin peptides considered to have immunomodulatory and anti-inflammatory effects via melanocortin receptors [60]. RCI has been grandfathered in for FDA-approval for DM and PM since 1952 but data remains limited regarding its efficacy [60].

In an open-label study including 9 patients, ACTH gel was shown to be effective, safe, and well-tolerated for refractory cutaneous symptoms of DM [61]. At 3 months, 7 of 9 patients had improved CDASI scores and at 6 months, all 7 patients who continued treatment had improved CDASI activity scores with an average decrease of 13.4 points from baseline [61].

A prospective pilot clinical trial primarily focused on muscle disease recruited 11 patients with refractory, active disease, with 10 completing the study [60]. Seven of the 10 patients met the primary end point defined by the IMACS definition of improvement at a median of 8 weeks [60]. There was a significant steroid dose reduction with RCI treatment from 18.5 mg/day to 2.3 mg/day at 24 weeks. It was deemed reasonably well tolerated and safe [60]. Despite these encouraging results, RCI is cost-prohibitive for many patients and therefore unlikely to become a first-line therapy [60].

Conclusion

Dermatomyositis presents a major therapeutic challenge despite efforts to optimize conventional therapeutics and develop new ones. This is largely due to the heterogeneity of the disease as well as our relatively limited understanding of the disease pathogenesis.

Conventional pharmacological therapy relies on a combination of antimalarials, corticosteroids, nonsteroidal immunosuppressives, and/or IVIg. However, because many patients remain refractory to treatment, new medications including biologics are being studied. It is critical we better understand our historical treatments as well as the new therapies emerging from both a clinical and translational standpoint in order to more effectively treat patients, particularly those who are refractory to current therapies.

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Compliance with ethical standards

Competing Interests The authors are employed by the University of Pennsylvania, which owns the copyright for the CDASI. VPW is the principal investigator of Lenabasum in DM.

Abbreviations *ARS*, aminoacyl-tRNA synthetase; *AZA*, Azathioprine; *CQ*, Chloroquine; *CADM*, Clinically amyopathic dermatomyositis; *CDM*, Classic dermatomyositis; *cAMP*, cyclic adenosine monophosphate; *CsA*, Cyclosporine; *DM*, Dermatomyositis; *HCQ*, Hydroxychloroquine; *IFN*, interferon; *IL*, interleukin; *IIM*, Idiopathic inflammatory myopathies; *IMACS*, International Myositis Assessment & Clinical Studies

Group; *ILD*, Interstitial lung disease; *IVIg*, Intravenous immunoglobulin; *MDA5*, anti-melanoma differentiation-associated gene 5; *MTX*, methotrexate; *MMF*, mycophenolate mofetil; *PDE-4*, phosphodiesterase-4; *PM*, polymyositis; *RP-ILD*, rapidly progressive interstitial lung disease; *RTX*, rituximab; *Q*, Quinacrine; *TAC*, Tacrolimus; *TNF*, tumor necrosis factor; *VAS*, visual analog scale

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