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Promising and Upcoming Treatments in Myositis

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Abstract

Purpose of Review—To highlight new and emerging treatment targets in myositis.

Recent Findings—The landscape of novel therapeutics in myositis has vastly changed in the past 5 years. This is largely due to a greater understanding of the pathogenesis of myositis and validation of more robust outcome measures that standardize the ability to assess treatment response. Clinical trials in dermatomyositis are leading the way with ongoing multicenter, international phase 3 clinical trials. Proof-of-concept studies targeting the JAK/STAT pathway have also showed early promise in treating refractory dermatomyositis in adults and children.

Summary—This review highlights that the future armamentarium of therapeutic drugs will likely be larger and more selective in treating different subgroups of myositis.

Keywords

Myositis; Dermatomyositis; Immune-mediated necrotizing myopathy; Novel treatments

Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of autoimmune disorders characterized by immune-mediated muscle injury that results in muscle inflammation and skeletal muscle weakness. Myositis can be challenging to manage because it commonly encompasses extramuscular manifestations such as skin, lung, and joint involvement. The four main subgroups of myositis that have been identified are dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), polymyositis (PM), and sporadic inclusion body myositis (sIBM) [1,2]. Overlap myositis including antisynthetase syndrome are increasingly being recognized as a separate entity [3]. While the classification criteria of myositis have evolved over the years, new treatments have lagged behind. Our current treatment modalities are based mostly on retrospective case

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series and case reports with a paucity of randomized controlled clinical trials. However, with the recently developed and validated ACR/EULAR Myositis Response Criteria [4] to assess treatment response coupled with advances in understanding the pathogenesis of myositis, there have been multiple promising treatments that we will highlight in this review.

Before discussing new and emerging therapies, we will briefly discuss current treatments commonly used in clinical practice and the studies that have demonstrated their efficacy.

Current Treatments in Myositis

While glucocorticoids are used in the acute management of myositis, steroid sparing agents are instituted simultaneously or early on the course of the disease. The key steroid sparing agents that are used in idiopathic inflammatory myopathies excluding inclusion body myositis will be discussed in this section (Table 1).

Methotrexate

Methotrexate (MTX) is known to inhibit several pathways including folic acid and purine metabolism as well as adenosine signaling [15]. Two important studies evaluated the efficacy of methotrexate and both demonstrated improved strength and significant reduction in prednisone requirement by an average of 30 mg/day [5, 6]. The latter study also noted a decrease in flares during the 2-year follow-up period [6]. Overall, both studies showed that oral methotrexate should be considered early in the treatment course of patients with DM and PM to improve strength and lower steroid requirement.

Azathioprine

Azathioprine (AZA) is a purine analog that blocks T cell and B cell proliferation [7]. In 1980, a single-center, prospective, double-blind, therapeutic trial of azathioprine as initial therapy for treatment of polymyositis was conducted using creatine kinase (CK) and strength as the primary outcome measures. The trial consisted of 16 patients who received 60 mg of prednisone daily plus azathioprine (2 mg/kg of body weight per day) or placebo with data measurements at 3 months, 1 year, and 3 years from onset [7]. At the 1-year mark, there was significant improvement in functional disability for the azathioprine group compared with prednisone monotherapy ($p < 0.01$) [8]. This study showed azathioprine was effective at improving strength and can be used as a steroid sparing agent given the ability of many patients to taper off prednisone.

Combination of Azathioprine and Methotrexate

In 1998, a randomized cross-over study of 30 patients demonstrated that combination therapy with methotrexate and azathioprine was effective at improving strength in patients who previously had inadequate responses to either MTX or AZA alone. Thirty patients were randomized to receive either a combination of weekly oral methotrexate and daily azathioprine or intravenous methotrexate with leucovorin rescue every 2 weeks for 6 months [16]. Most patients initially randomized to oral combination therapy improved 8/15(53%), whereas only 3/15(20%) initially randomized to IV MTX therapy showed improvement. Unfortunately, the study was not powered to directly compare treatments but the intention-

to-treat analysis showed a trend in favor of those patients who first received oral combination therapy ($p = 0.025$) [16].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a prodrug whose mechanism of action involves the inactivation of inosine monophosphate dehydrogenase, an enzyme in purine synthesis that results in the inhibition of T and B cell proliferation [17]. A case series of seven patients who met the Bohan and Peter criteria and previously failed MTX and/or AZA were given steroids and MMF which was titrated up to 1 g twice daily. All patients had improvement in CK and inflammatory markers while 6 of 7 (86%) patients had a marked improvement in their weakness [9]. Another study of 10 patients with DM treated with MMF in combination with steroids also demonstrated improvement in muscle strength as measured by manual muscle testing (MMT) and a substantial reduction in steroid requirement [10].

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) was first reported to be efficacious in polymyositis in 1987 [18] and used in the treatment of multiple neuromuscular disorders such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and myasthenia gravis [19]. In 1993, in a randomized, double-blind, placebo-controlled study, 15 patients with biopsy-proven, refractory dermatomyositis were treated with IVIG. Patients were treated with prednisone (mean 25 mg/day) and immune globulin (2 g/kg) divided in two doses or placebo every month for 3 months. Overall, 12 patients received IVIG and 75% had major improvement in muscle strength scores and neuromuscular symptoms, whereas none of the placebo-treated patients had major improvements and five had worsening of symptoms [11]. In 2012, in a randomized, double-blind, placebo-controlled study, 26 DM or PM patients refractory to steroids alone were treated with IVIG. The primary outcome was MMT, CK level, and activities of daily living. After the first 8 weeks, there was statistically significant improvement in MMT in the IVIG group compared with placebo [20].

Rituximab

Rituximab targets CD20-positive cells leading to the depletion of peripheral B cells. The Rituximab in Myositis (RIM) trial was a multicenter, randomized, double-blind, placebo trial in 195 adult and pediatric patients with refractory myositis to assess the safety and efficacy of rituximab. The primary outcome measure was the time to achieve the International Myositis Assessment and Clinical Studies Group preliminary definition of improvement (DOI) between the 2 groups [21]. While 161 of 195 patients (83%) of the randomized patients met the DOI, the primary outcome measure was not met [12]. Post hoc analyses demonstrated that patients with an autoantibody had a more robust response to rituximab than those who did not [22].

Cyclophosphamide

Cyclophosphamide is an alkylating agent that exhibits cytotoxic effect through cross-linking of strands of DNA and RNA and inhibition of protein synthesis. Given the toxic effects of this medication along with increased risk of malignancy, it has been mostly used for

refractory disease or severe lung manifestations. In 2007, a retrospective review looked at 17 DM and PM patients with severe lung disease treated with at least six doses of IV cyclophosphamide (300–800 mg/m^2) and steroids. Results demonstrated 11/17 patients had improvement in dyspnea and 8/17 patients had improvement in pulmonary function testing [23]. In 2013, a retrospective review was published of 9 DM/PM patients treated with monthly IV cyclophosphamide (1.0–1.5 g/m^2) and steroids. All nine patients demonstrated improvement in muscle strength and 8/9 saw their CK levels decrease [24].

Calcineurin Inhibitors

The most commonly used calcineurin inhibitors are cyclosporin and tacrolimus which both exert their therapeutic effects by inhibiting activation of T cells. Since the 1990s, there have been multiple case reports and retrospective studies highlighting their clinical benefits in the treatment of myositis and myositis-associated ILD. One of the earliest studies was in 1991 where it was reported that 3 patients with DM previously refractory to azathioprine were treated with cyclosporine and had remarkable improvement in muscle strength with the ability to taper prednisone dose [25]. In 2011, another case series of 14 patients with DM and associated acute/subacute interstitial pneumonia were treated with cyclosporine and prednisone. At the 1-year mark, 10/14 patients showed improvement in pulmonary function tests and CT findings, whereas 3/14 remained stable [26].

Tacrolimus has also been used to treat patients with refractory myositis with or without lung disease. A case series of 8 myositis patients (6 Jo-1 and 2 SRP) treated with tacrolimus demonstrated that all 8 had improvement in strength and reduction in CK levels. In particular, the Jo-1 antibody patients decreased their mean CK levels from 3114 to 87 IU/mL ($p < 0.01$) and daily prednisone dose by 80% [13]. In an observational study of 31 patients with polymyositis or dermatomyositis, tacrolimus also led to a decrease in CK levels approximately 2–4 months after initiation [14].

Promising Treatments in Myositis

The landscape of promising treatments in myositis has changed rapidly in the past 5 years. Some therapeutic drugs are in phases 3 clinical trials and others have shown early promise in proof-of-concept studies. In particular, dermatomyositis leads the way in novel treatment options with more momentum than other subgroups of myositis (Table 2). We will highlight the results of key promising treatments organized by subgroups of myositis.

Dermatomyositis

Lenabasum—Lenabasum is a cannabinoid receptor type 2 agonist that activates resolution of innate immune responses to reduce tissue inflammation and fibrotic processes [32]. First used in a clinical trial to treat skin disease in early diffuse cutaneous systemic sclerosis, a second indication, dermatomyositis, was added in 2017 [33]. In a 16-week phase 2 double-blinded, randomized, placebo-controlled study, 22 patients with classic or amyopathic dermatomyositis were compared with placebo with the primary efficacy outcome measured by the CDASI activity score. A key distinction in this study is that all subjects were allowed stable background therapy during the study period. Open-label extension (OLE) of 20/22

(91%) eligible subjects who received lenabasum up to week 68 demonstrated that improvement was seen in multiple physician- and patient-reported efficacy outcomes, in particular the validated CDASI activity score = − 21.8 (2.26), Patient Skin Activity VAS = − 3.0 (0.75), and Physician Overall Disease VAS = − 3.0 (SD) [27, 28]. Notable medication changes during the OLE included two participants who reduced MMF, two switched from MTX to MMF, one started MTX, and one person had a steroid burst with taper.

Currently, there is a phase 3 international multicenter, double-blind, randomized, placebo-controlled study assessing the efficacy and safety of lenabasum for the treatment of dermatomyositis (Clinical Trial Identifier NCT03813160). The primary efficacy outcome measure will be measured at week 52 by the validated Total Improvement Score (TIS), which is a weighted composite measure of improvement from baseline in six core set measures: Physician Global Assessment of Disease Activity, Physician Assessment of Extramuscular Disease Activity, Patient Global Assessment of Disease Activity, Health Assessment Questionnaire (patient-reported disability), manual muscle testing (MMT), and muscle enzymes. The study plans to enroll roughly 150 participants from about 60 sites including North America, Europe, and Asia. Subjects will be randomized to receive lenabasum 20 mg twice per day, lenabasum 5 mg twice per day, or placebo twice per day in a 2:1:2 ratio.

The success and favorable safety profile lenabasum showed in the phase 2 trial for dermatomyositis led to an orphan drug designation for this disease as well as systemic sclerosis and others [34]. This designation is unique in that it is given to drugs intended to treat, diagnose, or prevent diseases that affect less than 200,000 people in the USA. If the phase 3 study demonstrates similar results with improvement in cutaneous and muscular disease activity, it may be the first drug to reach FDA approval for dermatomyositis.

Abatacept—Abatacept is a recombinant fusion protein made of the cytotoxic T lymphocyte antigen 4 (CTLA4) and a fragment of the Fc domain of human IgG1 that competes with CD28 for CD80 and CD86 binding and thus able to modulate T cell activation [35]. Abatacept was recently used as treatment for myositis in a randomized, phase IIb treatment delayed-start trial. The primary outcome measure was the percentage of patients who met the defined International Myositis Assessment and Clinical Studies Group definition of improvement (DOI), after 6 months of treatment. A secondary outcome measure was the number of responders in the early treatment arm compared with the delayed treatment arm at 3 months. Inclusion criteria included definitive diagnosis of DM or PM via muscle biopsies along with measurement of autoantibodies. Of the 19 participants included in the analysis, 8 achieved the DOI at 6 months [29•]. There were eight AEs regarded as related to the drug, four mild and four moderate, and three serious AEs but none related to the drug. Other notable findings included a significant increase in regulatory T cells compared with other markers that were unchanged in repeated muscle biopsies.

Currently, there is a phase 3 randomized, double-blind clinical trial underway to evaluate the efficacy and safety of abatacept in combination with standard therapy compared with standard treatment alone in patients with active idiopathic inflammatory myopathy (Clinical Trial identifier NCT02971683). The primary outcome measure will be the number of

participants who achieve the validated International Myositis Assessment and Clinical Studies (IMACS) definition of improvement (DOI) at week 24. The study plans to enroll roughly 150 participants from about 98 sites including North and South America, Europe, and Asia. Subjects will be randomized to receive abatacept weekly in addition to the subject's current standard treatment or placebo for 24 weeks. After which, both arms will then complete a 28-week open-label period of abatacept treatment plus the subject's current standard treatment. Lastly, there is a study in progress evaluating abatacept in patients with refractory JDM (Clinical Trial identifier NCT02594735).

Janus Kinase Inhibitors—The Janus kinases (JAK) are cytoplasmic protein tyrosine kinases that are critical for signal transduction to the nucleus and affect downstream mediators of interferon activity [36]. There have been multiple reports of its efficacy in autoimmune dermatologic conditions such as alopecia areata and sarcoidosis [37, 38]. Tofacitinib, the first pan-JAK inhibitor to be FDA-approved to treat rheumatoid arthritis, has now been joined by more JAK-1 selective inhibitors such as baricitinib and upadacitinib.

JAK inhibitors have also shown early promise in refractory dermatomyositis. The first case report was a 72-year-old female with severe refractory dermatomyositis with a CDASI of 30 and minimal response to high-dose steroids, azathioprine, and IVIG, who was treated with ruxolitinib for myelofibrosis [39]. Following the initial case report, several case reports and series evaluated the efficacy of tofacitinib in skin predominant refractory disease [40, 41]. In a case series of 3 patients who failed multiple other steroid sparing agents, the clinical response was observed after only 4 weeks. Of the three patients, two were on monotherapy with tofacitinib and the other one was in conjunction with hydroxychloroquine and the medication as well tolerated with no observed adverse events [42•]. Similarly, ruxolitinib has also been reported to be successful in treating 4 refractory dermatomyositis patients in France with improvement in skin and muscle disease [43].

A single-center open-label 12-week proof-of-concept study was conducted to evaluate the efficacy and safety of tofacitinib for treatment of refractory DM [30]. There were 10 patients who failed at least 2 steroid sparing agents or high-dose steroids. Patients were not allowed any other steroid sparing agents which were washed out before entry. The primary outcome was the DOI at 12 weeks as defined by the International Myositis Assessment and Clinical Studies (IMACS) as improvement of ≥ 20% in 3 of 6 core set measures (CSM) with no more than 2 worsening by ≥ 25%. The response rate was also measured by the ACR/EULAR Myositis Response Criteria. The secondary outcome measures were the CDASI, steroid sparing effect of tofacitinib, safety, and tolerability. All 10 patients who received tofacitinib 11 mg XR daily met the DOI at 12 weeks. The median TIS was 40 (IQR 32.5, 47.5) indicative of at least moderate improvement. The mean change in CDASI activity score showed clear improvement from baseline to 12-week time point (28 ± 15.4 (baseline) vs. 9.5 ± 8.5 (12 weeks); $p = 0.0005$) [30]. Secondary outcomes such as the ability to taper prednisone were reported in 3 of 4 (75%) who were on prednisone at entry. Furthermore, key chemokines such as CXCL 9/10 were downregulated with treatment. Currently, there is a 1-year treatment extension of this study.

A recent 2019 case report was published that highlighted the effectiveness of baricitinib in treating a refractory case of juvenile dermatomyositis (JDM) [44]. An 11-year-old male who was diagnosed with JDM at age 3 with classic skin and muscle findings failed numerous therapies including cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, infliximab, adalimumab, rituximab, tacrolimus, cyclosporine, and IVIG in the first 7 years of his disease course. Before starting baricitinib, he required high doses of steroids (2 mg/kg) for severe skin disease including progressive calcinosis [44]. After 6 months of treatment, there was improvement in his skin disease with no new calcinosis lesions. Treatment with baricitinib also reduced biomarkers of IFN signaling and type 1 IFN-induced gene expression.

Additionally, a larger case series reported four patients with refractory JDM treated with baricitinib for 24 weeks [45]. All immunosuppressant medications outside of IVIG were washed out prior to treatment and the primary outcome measure was reduction in symptom daily diary score (DDS) of weakness, fatigue, musculoskeletal pain, and rash. The preliminary data demonstrated all patients improved in the symptom DDS score and the 2 patients with baseline weakness showed improvement in muscle strength [45].

Eculizumab—Eculizumab is a monoclonal antibody directed against C5 which blocks the generation of C5a and membrane attack complex (MAC) assembly [46]. There have been two case reports of young women with evidence of JDM based on labs, clinical exam, and muscle biopsy that failed conventional DMARDs but had recovery with use of eculizumab [47, 48]. The one confounding diagnosis present in both cases was suspected thrombotic microangiopathy with severe kidney injury. In 2000, a pilot study was conducted to evaluate the safety and efficacy of eculizumab on 13 patients with dermatomyositis undergoing concomitant treatment with moderate doses of methotrexate or steroids. Unfortunately, the only data released showed the drug had a favorable safety and tolerability profile but no information released about subjects' clinical response to the medication [46].

Rituximab—A post hoc analyses of the RIM trial assessed the efficacy of rituximab for the cutaneous manifestations of adult DM and JDM [31]. In this analysis, results showed significant improvement in cutaneous disease activity at the end of the trial after receiving rituximab compared with baseline for both DM (78 patients) and JDM groups (48 patients). The cutaneous visual analog scale activity improved in both adult DM and JDM. Adult DM patients who were in the early rituximab arm tended to have a faster improvement in skin disease compared with those in the late arm though not statistically significant with a median time to improvement of 16 weeks ($p = 0.052$) [31]. Unfortunately, the CDASI was not utilized at the time of the RIM trial and therefore, the assessment of the skin disease was based on a cutaneous visual analog scale.

Immune-Mediated Necrotizing Myopathy (IMNM)

Intravenous Immunoglobulin—A case series was published of three patients who were anti-HMG-CoA reductase antibody (anti-HMGCR)–positive who declined glucocorticoid for treatment of their myositis due to concerns for side effects given the comorbid condition of diabetes mellitus [49]. These patients received monotherapy with IVIG at dose of 2 g/kg

per month. The primary outcome measures were reduction in CK levels and improvement in strength. Prior to administration of IVIG, the mean creatinine level was 4919 ± 3523 IU per liter (ref 32–232) and all patients had demonstrable proximal upper and lower extremity weakness ranging from 2/5 to 4/5 on the MRC scale. After receiving at least two rounds of IVIG, the mean CK level declined to 1125 ± 1101 IU per liter, quantitative dynamometry of arm abduction improved from baseline mean of 3.5 to 6.2 kg, and hip-flexion strength increased significantly and even normalized for 2 of 3 (67%) patients (Table 3). No adverse events were noted with therapy and no additional agents were added. Similarly, 6 Australian subjects with anti-HMGCR in a case series were treated with IVIG. Initially, all subjects were steroid responsive, but 5 relapsed when steroids were weaned below 10 mg/daily. Both CK and clinical strength improved with restarting of steroids and IVIG. In all 5 cases, clinical remission was achieved with this combination, 4 of whom were also on varying background immunosuppressive therapies [53]. Most recently, in this past year, a large retrospective cohort study of 55 patients with statin-induced anti-HMGCR myopathy treated with IVIG was published. Of the 55 patients, 41 received steroids in addition to IVIG and 14 received IVIG monotherapy. Results demonstrated all 14 IVIG monotherapy patients achieved remission and 37/41 in the combination group achieved remission at 6 months [50••].

Rituximab—A retrospective review of the longitudinal course of SRP-positive patients in the myositis cohort at Johns Hopkins Myositis Center was published. The study analyzed 37 patients who were SRP antibody–positive and have multiple clinic visits between 2002 and 2015 with detailed data of immunosuppressive regimens. The primary outcome measures were CK levels and strength. Of the 37 patients with SRP positivity, only 21 received rituximab for their treatment and 17 were included in analysis as 4 were lost to follow-up [51]. Thirteen of these patients had a positive response with improvement in weakness and CK levels. However, only half of patients returned to near-full or full strength after 4 years of treatment and many still had elevated CK levels.

A recent case series was published of three patients with refractory anti-HMGCR patients who found success with rituximab treatment [52]. All patients had been exposed to atorvastatin prior to presentation and had a mean CK of 6634 and these patients were refractory to high-dose prednisone, methotrexate, cyclosporine, and IVIG. Patients were treated with an induction dose of 375 mg/m^2 every week for 4 weeks, followed by a maintenance dose of 375 mg/m^2 every month. Further rituximab dosing was based on individual patient response. All patients had normalization of their CK levels and significant reduction or normalization of HMG-CoA antibody levels after treatment.

Inclusion Body Myositis

Bimagrumab—This drug is a monoclonal antibody directed against type 2 activin receptors; the inhibition of this signaling pathway increases protein synthesis, stimulates skeletal muscle growth, and increases muscle function and strength [54]. The RESILENT trial was a large randomized, double-blind, placebo-controlled phase 2b study to assess the safety, efficacy, and tolerability of intravenous bimagrumab in 251 patients with inclusion body myositis from 38 different academic centers worldwide [55]. Inclusion criteria were a

diagnosis of inclusion body myositis per modified 2010 MRC criteria and ability to walk at least 1 m without assistance from another individual (assistive devices allowed). Participants were mostly male (~ 65%) with a mean age of 69 and were randomly assigned in a block of four schedule (1:1:1:1) to either bimagrumab (10 mg/kg, 3 mg/kg, or 1 mg/kg) or placebo, administered as intravenous infusions every 4 weeks for at least 48 weeks. The primary outcome measure was improvement in 6-min walk distance (6MWD) along with drug safety and tolerability. Unfortunately, after 52 weeks, there was no difference in the 6MWD change from baseline for any of the bimagrumab groups compared to the placebo. Furthermore, there was no improvement in muscle strength, grip strength, or pinch strength. Despite these negative findings, in the 10 mg/kg dose group, bimagrumab improved lean body mass and self-reported physical function. While the published results were disappointing since it was one of the largest studies in IBM, it also highlighted the need for more refined functional outcome measures to ascertain the therapeutic effects of drugs in inclusion body myositis.

Rapamycin—Rapamycin is an inhibitor of the mechanistic target of rapamycin (mTOR), a protein kinase that regulates several intracellular processes including survival, protein synthesis, and autophagy [56]. A prospective, randomized, double-blind, placebo-controlled phase 2b trial of rapamycin was conducted in 44 patients with IBM at a single center in France over the course of 12 months. The primary outcome measure was quadriceps strength using quantitative muscle testing and 6MWD as a secondary outcome. Results showed no difference in quadriceps strength after 1 year between the 22 subjects who received treatment and 22 participants in the placebo arm with a mean relative change of −11.07% vs −12.36% respectively [56]. However, there was less fatty replacement of muscle in the quadriceps and hamstrings as assessed by MRI along with improvement in 6MWD in the treatment group compared with placebo.

Arimoclomol—Arimoclomol prolongs the activation of heat shock factor 1 selectively in stressed cells and, subsequently, augments heat shock protein (HSP) levels [57, 58]. Previously, a small randomized controlled trial evaluating the drug's safety was conducted in 24 sIBM patients, where 18 participants received arimoclomol 100 mg PO TID for 4 months and 8 received placebo [59]. The results demonstrated arimoclomol to have a favorable safety profile and at 1 year the IBM functional rating scale (IBMFRS) decline was less in the treatment group compared with that in the placebo with the p value approaching significance at 8 months [59]. Currently, there is a phase 2/3 randomized, double-blind, placebo-controlled trial in progress to evaluate arimoclomol for the treatment of sIBM (Clinical Trial Identifier NCT02753530). The study plans to enroll roughly 150 participants from at least 11 sites in the USA and the UK. Subjects will be randomized to receive arimoclomol 400 mg TID or placebo for 20 months. The primary outcome measure is the IBMFRS and several notable secondary outcome measures are MMT and maximum voluntary isometric contraction (MVICT) of the quadriceps.

Conclusion

Our current treatment options for myositis have been relatively stagnant for the past 20 years. While current drugs are efficacious in treating myositis, it is not uncommon for recurrent flares and inability to induce remission of the disease. Fortunately, in the past 5

years, the landscape of promising treatments in myositis has changed especially with the development and validation of more robust outcome measures that standardize the ability to assess treatment response. Novel therapeutics in dermatomyositis lead the way with the number of ongoing trials and positive results. Sporadic inclusion myositis remains a challenging disease to treat, but several studies evaluating the degenerative pathway are showing promise. The future of myositis treatment is one filled with much anticipation and excitement especially since results from these trials may lead to the first FDA-approved drug for the treatment of myositis.

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•• Of major importance

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Table 1

Current treatments in myositis and the evidence supporting it efficacy

Drug	Type of Study	No. of patients who received treatment	Type of myositis	Dose	Concomitant steroid use	Treatment response (%)	Source
Methotrexate	Retrospective	55	DM, PM, and IBM	Minimum dose 5 mg/week methotrexate	Yes	Overall clinical response as measured by muscle strength. Complete response: 9/55(9%). Partial response: 31/55(56%)	Joffe [5]
	Retrospective	12	DM and PM	Mean maximum dose 14.4 mg (range 7.5–20 mg/week)	Yes	11/12 (92%) of patients had improvement in muscle strength as measured by MMT, reduction in CK levels. Prednisone taper was also tolerated at 3–12 months	Newman [6]
Azathioprine	Prospective, double-blind	8	PM	2 mg/kg of body weight per day)	Yes	8/8 (100%) of patients treated with azathioprine had reduction in CK levels and prednisone use and improvement in functional disability at 12 months	Bunch [7, 8]
Mycophenolate mofetil	Case series	7	DM and PM	1 g twice a day	Yes	6/7 (86%) of patients responded with improved proximal muscle strength and reduction in CK levels, inflammatory markers, prednisone usage, and skin rash for DM patients at 6 months	Majithia [9]
	Case series	10	DM	1 g twice a day	Yes	6/10 (60%) of patients completely tapered off steroids and improved MMT scores at 12 months	Rowin [10]
IVIG	Randomized, double-blind, placebo-controlled	12	DM	2 g/kg over 2 days	Yes	9/12 (75%) had improvement in mean MRC, reduction in CK levels, and improvement in skin rash at 3 months	Dalakas [11]
Rituximab	Randomized, double-blind, placebo-controlled trial	195	DM, JDM, and PM	Based on BSA: children with BSA < 1.5 m^2 received 575 mg/m^2 per infusion; adults and children with BSA of 1.5 m^2 received 750 mg/m^2 up to 1 g per infusion	Yes	161/195 (83%) of participants achieved DOI at 44 weeks, but the primary outcome was not achieved.	Oddis [12]
Tacrolimus	Case series	8	PM (6 anti-Jo-1-positive, and 2 SRP-positive)	0.075 mg/kg daily in twice daily doses	Yes	8/8 (100%) had improvement in muscle strength and 5/6 (83%) Jo-1-positive regained normal strength. 2/2 (100%) of the SRP-positive patients had improved strength	Oddis [13]
Cyclophosphamide	Case series	9	DM/PM	1000–1500 mg/m^2	Yes	9/9 (100%) improved and became asymptomatic after a mean period of 12 months	Mitsui [14]

DM dermatomyositis, *PM* polymyositis, *JDM* juvenile dermatomyositis, *BSA* body surface area, *CK* creatine kinase, *DOI* definition of improvement, *MMT* manual muscle testing

Table 2

Promising treatments in dermatomyositis

Drug	Type of Study	No. of patients who received treatment	Dose	Concomitant steroid use	Concomitant Steroid sparing agents	Treatment response (%)	Source
Lenabasum	Phase 2 double-blinded, randomized, placebo-controlled	20	20 mg BID	Yes	Yes	13/18 (72%) achieved low skin disease activity (CDASI ≤ 14) at week 68	Werth [27, 28]
Abatacept	Phase 2 randomized, treatment delayed-start trial	19	Weight-based dose individuals weighing < 60 kg received 500 mg, those 60–100 kg received 750 mg, and those > 100 kg received 1000 mg.	Yes	Yes	8/19 (42%) achieved the DOI at 6 months	Tjamlund [29]
Tofacitinib	Single-center open-label prool-of-concept study	10	11 mg XR daily	Yes	No	10/10 (100%) met the primary outcome DOI at 12 weeks, with 50% demonstrating moderate improvement and 50% having minimal improvement based on the TIS	Paik [30]
Rituximab	Randomized placebo-phase--controlled trial (post hoc analyses)	120	Based on BSA: children with BSA < 1.5 m^2 received 575 mg/m^2 per infusion; adults and children with BSA of 1.5 m^2 received 750 mg/m^2 up to 1 g per infusion	Yes	Yes	The cutaneous visual analog scale activity improved in adult DM (3.22 1.72, p = 0.0002) and JDM (3.26 1.56, p < 0.0001) at 44 weeks	Aggarwal [31]

Table 3

Promising treatments in immune-mediated necrotizing myopathy

Drug	Type of Study	No. of patients who received treatment	Dose	Concomitant steroid use	Concomitant steroid sparing agents	Treatment response (%)	Source
IVIG	Case series of HMGCR patients	3	2 g/kg per month	No	No	3/3 (100%) showed improvement in CK levels, muscle strength including quantitative dynamometry of arm abduction, and anti-HMG-CoA reductase antibody titers at 2 months	Mammen [49]
	Retrospective cohort	55	2 g/kg per month	Yes (41 of 55)	Yes	Steroid free induction strategy 14/55 (25%) achieved remission with either steroid sparing agent ($n = 7$) or dual IVIG/steroid sparing agent ($n = 7$)	Meyer [50]
Rituximab	Case series SRP patients	17	Varied among patients not listed	Yes	Yes	13/17 (76%) improvement in weakness and CK levels at 24–48 months	Pinal-Fernandez [51]
	Case series HMGCR patients	3	Induction dose of 375 mg/m^2 every week for 4 weeks, followed by a maintenance dose of 375 mg/m^2 every month	Yes	Yes	3/3 (100%) normalization of CK and significant reduction or normalization of HMG-CoA antibody levels at 12 months	Zhang [52]