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# Current and new targets for treating myositis

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**Abstract**

As treatment of refractory idiopathic inflammatory myopathies (IIM) has been challenging, there is growing interest in assessing new therapies that target various pathways implicated in the pathogenesis of IIM. In the largest clinical trial to date, rituximab was studied in adult and juvenile myositis, but the primary outcome was not met despite 83 percent of subjects with refractory myositis meeting the definition of improvement. The U.S. Food and Drug Administration (FDA) has recently granted approval to Octagam 10% immune globulin intravenous (IVIg), for the treatment of adult dermatomyositis based on impressive results from a double-blind placebo-controlled trial. Anti-tumor necrosis factor (anti-TNF) utility in IIM is not recommended and recent reports suggest this therapy may induce systemic autoimmune disease including myositis. Further, anti-IL6 therapy cannot be recommended as a recent trial of tocilizumab failed to reach its primary endpoint.

Further studies are needed to assess the role of newer therapies such as abatacept (inhibition of T cell co-stimulation), sifalimumab (anti-IFNα), Janus kinase [JAK] inhibitors, apremilast (phosphodiesterase 4 inhibitor), and KZR-616 (selective inhibitor of the immunoproteasome) given their biological plausibility and encouraging recent small-case series results. The future of IIM therapy will depend on exploring biomarkers implicated in the etiopathogenesis of IIM, improvements in myositis classification based on serological and histopathological features, and well-designed controlled clinical trials using validated consensus outcome measures.

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## Introduction

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic autoimmune rheumatic diseases that include adult polymyositis (PM), adult dermatomyositis (DM), myositis in overlap with other systemic autoimmune rheumatic diseases or cancer, juvenile myositis (dermatomyositis more than polymyositis), inclusion body myositis (IBM), and necrotizing autoimmune myopathy.

The treatment of IIM is very challenging as the disease is rare and the variable clinical phenotypes make it difficult to assess treatment efficacy. Further, there are a small number of published randomized, double-blind clinical trials [1–4]. Traditional treatment approaches include glucocorticoids and conventional immunosuppressive or immunomodulatory agents such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, and IVIg. There has been growing interest in assessing novel biologic therapies that target various pathways implicated in the etiopathogenesis of myositis. Biomarkers involved in the pathogenesis of IIM have been explored using cytokine/chemokine analyses, microarrays, and RNA-sequencing analysis, advanced immunohistochemistry, and flow cytometry. Novel classification schemes for IIM based on serological and histopathological features may also enhance the design of clinical trials and subject enrollment [5,6]. Additionally, in the past several years, consensus and data-driven core set measures (CSM) have replaced poorly-standardized muscle strength and functional assessments for evaluation of myositis disease activity and damage. In particular, two international groups, the International Myositis Assessment and Clinical Studies (IMACS) Group and the Pediatric Rheumatology International Trials Organization (PRINTO), have defined and validated consensus CSM for adult and pediatric populations [7–9]. These consensus outcome measures along with active international initiatives to develop both data- and consensus-driven response criteria will assist in studying novel therapies in a more systematic and rigorous fashion [10].

In this chapter, we review potential therapeutic targets and the immunomodulatory and immunosuppressive therapies currently used to treat the various subsets of

inflammatory myopathy as well as myositis-associated interstitial lung disease (ILD).

## Rituximab

Rituximab, a B cell depleting agent, is a monoclonal antibody against the CD20 antigen on B lymphocytes. The efficacy of rituximab in refractory myositis has been suggested in several small case reports and case series [11−15]. In a small, open-label, uncontrolled, pilot trial of rituximab therapy (4 weekly IV doses) in 6 treatment-resistant DM patients, all subjects had major clinical improvement in muscle strength and rash [16]. In another small open-label trial of rituximab in 4 patients with refractory PM, all patients demonstrated return of full muscle strength and a significant decline in serum creatine kinase (CK) levels [17]. However, an open-label trial of rituximab in 8 DM patients showed no cutaneous improvement and the serum CK did not significantly change and only three patients demonstrated modest improvement in muscle strength [18].

In the largest randomized, double-blind, controlled clinical trial in IIM [the Rituximab in Myositis (RIM) Trial], 195 patients (75 with PM, 72 with DM, and 48 with JDM; all refractory to glucocorticoid therapy and at least one immunosuppressive drug) were randomized to receive two 1-g rituximab infusions (14 days apart) either at baseline or 8 weeks later [1]. Entry criteria included fairly significant muscle weakness (not required in the juvenile DM patients) and $\geq 2$ additional abnormal consensus CSM for adults and $\geq 3$ abnormal CSM with or without muscle weakness for the pediatric subjects. Glucocorticoid and/or immunosuppressive therapy was allowed at study entry. The primary end point was the time to achieve the IMACS definition of improvement (DOI) which was compared between the rituximab early and rituximab late groups. Although the early rituximab group demonstrated no faster response to therapy than the group receiving rituximab later (failing to meet the primary outcome), the DOI was met by 83 percent of this refractory group of IIM patients with a median time to achieving the DOI of 20 weeks. Rituximab was also associated with a significant steroid-sparing effect as the mean prednisone dose decreased from 20.8 mg at baseline to 14.4 mg daily at the end of the clinical trial. Additionally, patients who initially met the DOI and who were subsequently re-treated with rituximab after a disease flare responded to rituximab retreatment as well. Rituximab therapy was generally well-tolerated and the most common adverse effects were infections. Additional studies derived from the RIM Trial demonstrated that the presence of anti-synthetase and anti-Mi-2 autoantibodies along with the juvenile DM subset, and lower disease damage were strong predictors of clinical improvement and response to B cell depletion therapy [19]. In a more recent analysis of the RIM trial data, significant improvements were noted in cutaneous disease activity after the addition of rituximab to the standard therapy in adult DM and JDM subjects [20]. The cutaneous visual analog scale activity improved in adult DM (3.22−1.72, $p = 0.0002$) and JDM (3.26−1.56, $p < 0.0001$), with erythroderma, erythematous rashes (without secondary changes of ulceration or necrosis), heliotrope, Gottron sign and papules improving most prominently.

The efficacy data of rituximab therapy specific to myositis-associated interstitial lung disease (MA-ILD) is limited to uncontrolled studies [13,14]. In a retrospective study of 50 patients with severe, progressive ILD (10 with MA-ILD), rituximab therapy resulted in a median improvement in forced vital capacity (FVC) of 6.7% ($p < 0.01$) and stability of the diffusing capacity of the lungs for carbon monoxide (DLCO); 0% change; $p < 0.01$) in the 6−12-month period after rituximab use [21]. Among the autoimmune ILD (AILD) patients included in this study, the best results were observed in patients with MA-ILD as 5 of the 10 (50%) patients demonstrated an increase in their FVC >10% and/or an increase in their DLCO > 15%, as compared to 4 out of 22 (18.2%) patients with other AILDs ($p = 0.096$). In a retrospective study from Norway, 24 patients with anti-synthetase syndrome (anti-SyS) and severe ILD with more than 12 months follow-up (median 52 months) post-rituximab, demonstrated improvements in FVC, forced expiratory volume in 1 s (FEV1) and DLCO of 24%, 22% and 17%, respectively [22]. The best outcome (> 30% improvement in all three PFT parameters) was observed in 7 patients with disease duration < 12 months and/or an acute onset/exacerbation of ILD. High-resolution CT (HRCT) findings also improved with a 34% (median) reduction in a predetermined ILD "score" and manual muscle testing (MMT8 score) and the serum CK also significantly improved. Interestingly, all subjects demonstrated a decrease (33%; $p < o.008$) in their anti-Jo-1 levels after rituximab. One limitation of the study was combined therapy with another immunosuppressive agent as 10 of the 12 patients also received cyclophosphamide making it difficult to attribute the response to rituximab therapy alone. There were 7 deaths among the 34 rituximab-treated patients (mortality rate comparable to that of the remaining anti-SyS cohort), 6 with infections (including 3 with p. jirovecii pneumonia). In a recent multicenter, open-label, phase II trial, 10 anti-SyS patients with MA-ILD refractory to traditional treatments (prednisone and at least 2 immunosuppressive agents), received 1 g of rituximab at day 0, day 15, and 6 months later [23]. Seven patients demonstrated an increase of at least 4 points on the MMT10 and the total CK level declined from 399 IU/L (range, 48-11,718) to 74.5 IU/L (range, 40−47,857). Rituximab therapy was associated with a significant steroid-sparing effect as the mean prednisone dose decreased from 52.5 mg/day (range, 10−70) at baseline to 9 mg/day (range, 7−65) along with a

concomitant decrease in the associated immunosuppressive therapy. ILD (FVC and/or DLCO) improved in 5 and stabilized in 4. In another recent retrospective study of anti-Jo1 antibody positive patients, 17 received rituximab and 30 patients were treated with conventional immunosuppressive agents and followed for a mean of 35 and 84 months, respectively [24]. Sixteen of the 17 receiving rituximab demonstrated a more rapid and marked response.

Rituximab [(375 mg/m$^2$ at 0 and 14 days) or 100 mg weekly for 4 weeks (low dose)] was given to 11 patients with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive DM with ILD [73% with rapidly progressive ILD (RP-ILD)] [25]. The more conventional dosing regimen led to complete remission in 2 patients (18%) with mild ILD and improvement in lung HRCT and/or lung function in 6 (55%). Lower dose rituximab therapy resulted in improvement in skin rash in 4 patients (100%) and ILD in 3 (75%). Infection episodes occurred in four (57%) and one (25%) of the conventional-dose and low-dose groups, respectively. Overall, the study suggested efficacy for rituximab in treating skin rash and ILD or RP-ILD in anti-MDA5-positive DM with low-dose rituximab being a useful option with fewer side effects. In another report, a 45-year-old woman with anti-MDA5-positive DM presented with myalgia, Gottron papules with ulceration, and dyspnea [26] with HRCT suggesting RP-ILD within the first month after diagnosis. Combination therapy with rituximab, tofacitinib and pirfenidone resulted in significant and sustainable improvement in cutaneous, pulmonary and radiographic changes.

A 76-year-old woman with muscle weakness, dyspnea, Raynaud phenomenon, hand arthropathy and anti-signal recognition particle (anti-SRP) and anti-SSA-positivity characterized as immune-mediated necrotizing myopathy in overlap with systemic sclerosis overlap syndrome [27] deteriorated on high dose glucocorticoids and intravenous gamma globulin. Her HRCT revealed a non-specific interstitial pneumonia pattern and her FVC was 93% with a DLCO of 65% predicted. After rituximab, she demonstrated an excellent and sustained response in both muscle and lung function that was sustained after 12 months.

## Intravenous immune globulin (IVIg)

IVIg is an immunomodulatory agent whose mechanism of action in the suppression of immune-mediated processes is not entirely elucidated. Many years ago, IVIg first demonstrated efficacy in DM in a double-blind, controlled trial in 15 patients with refractory DM [3]. In another open label trial with thirty-five PM patients, IVIg therapy was associated with significant clinical improvement in 70% of the patients, and the efficacy was maintained in half the patients 3 years after stopping IVIg [28]. An alternative subcutaneous form of IVIg in seven patients (4 DM, 3 PM) was associated with significant improvement in CK, muscle strength, and quality of life as well as discontinuation of immunosuppressive agents and reduction of the maintenance prednisone dose in all patients [29]. Subcutaneous IVIg was administered by a programmable pump and the patient's usual IVIg monthly dose was divided into equal doses given subcutaneously at weekly intervals. In a more recent randomized double-blind placebo-controlled trial in Japan, 26 subjects (16 PM and 10 DM) were randomly assigned to receive either IVIg therapy with polyethylene glycol-treated human IgG or placebo. Statistically significant improvements in the primary endpoint (manual muscle test score) and secondary endpoints (serum CK level and activities of daily living score) were noted in both IVIg and placebo groups [30]. Few case reports have suggested efficacy for IVIg in the treatment of myositis-ILD [31,32]. In one report, a patient with amyopathic dermatomyositis-associated ILD refractory to high-dose glucocorticoids and cyclosporine A, showed a good response to IVIg therapy [33]. The 2012 American Academy of Neurology guidelines support IVIg therapy for refractory DM but note insufficient evidence to support or refute its use in PM [34]. More recently, the ProDERM (Progress in DERMatomyositis) study evaluated the efficacy, safety, and long-term tolerability of IVIg (Octagam 10%) in patients with DM in a randomized, placebo-controlled, double-blind, Phase III study [35]. The positive results of the trial will soon be published and the favorable results led to the approval of this agent by the U.S. Food and Drug Administration (FDA) for the treatment of adult dermatomyositis.

IVIg is usually administered as infusions of 2 g/kg monthly but the dose or interval can be changed based on the disease severity and treatment responsiveness. A major advantage of IVIg is that it is safe in the setting of active infection and can also be used concomitantly with other immunosuppressive agents. The high cost of IVIg may influence decisions on its long-term use. Therefore, IVIg is generally reserved for patients with prominent dysphagia and refractory disease including marked cutaneous features or as salvage therapy in patients with severe and progressive MA-ILD resistant to conventional immunosuppressive therapy.

## Tocilizumab

Since the approval of tocilizumab, an antagonist of the interleukin-6 (IL-6) receptor, for the treatment of rheumatoid arthritis, there has been growing interest in evaluating its potential efficacy in other systemic autoimmune rheumatic diseases including myositis.

In the first report of tocilizumab use in IIM, two patients with refractory PM demonstrated improvement in the total CK level and MRI of their thigh muscles [36]. In

another report, a 32-year-old Japanese patient with an overlap syndrome, including features of DM (proximal muscle weakness, heliotrope rash, and Gottron sign) and systemic sclerosis, inflammatory arthropathy and CCP positivity (refractory to cyclosporine, IV cyclophosphamide, IVIg, tacrolimus, and combination methotrexate and adalimumab) was treated with tocilizumab which resulted in resolution of the DM rash and arthritis with gradual improvement in the muscle weakness and CK elevation allowing glucocorticoid tapering [37]. In a more recent report, a 43-year-old Chinese man with anti-MDA5 and anti-Ro52-positive DM presented with classic skin rashes, symmetric proximal muscle weak and progressive dyspnea [38]. HRCT of the chest demonstrated interlobular septal thickening and subpleural ground-glass opacities. Oral high dose prednisone, cyclophosphamide and tacrolimus led to disappearance of skin lesion and muscle weakness but the chest HRCT showed a rapid progression of interstitial lesions. Rescue IV methylprednisolone pulse therapy and addition of tocilizumab resulted in recovery and normalization of the ILD. In an open-label pilot study of tocilizumab in IMNM, a total of 11 patients with refractory IMNM were enrolled in the study, including 3 anti-3-hydroxy-3-methylglutaryl-CoA reductase- and 8 anti-SRP-positive patients [39]. Seven (63.6%) of these patients achieved clinically significant responses according to the 2016 ACR-EULAR myositis response criteria. Baseline serum IL-6 levels and the percentage of CD56-positive muscle fibers were positively correlated with the total improvement score after 6 months of tocilizumab treatment.

An investigator-initiated (University of Pittsburgh) multi-center, randomized, double-blind, controlled trial recently assessed the efficacy of tocilizumab in refractory adult PM and DM (clinicaltrials.gov, NCT02043548). Unfortunately, the trial failed to meet the primary and secondary endpoints and the results will be formally published in 2022.

## Abatacept

CD28 and CTLA-4, costimulatory molecules, have been reported to be up-regulated in the muscles of PM and DM patients [40,41]. Abatacept, which targets CD80 and CD86 on antigen presenting cells, was reported to be successful in a patient with refractory PM [42]. A child with severe recalcitrant JDM with ulcerative cutaneous disease and progressive calcinosis also demonstrated a favorable response to combination therapy with abatacept and sodium thiosulfate [43]. In another case report from Japan, abatacept therapy was associated with a favorable outcome in an anti-SRP positive patient with refractory myositis [44]. In a more recent report from Europe, a patient with severe myositis in overlap with rheumatoid arthritis, peripheral vasculitis and ILD, refractory to several traditional and biologic therapies, responded well to abatacept with good control of myositis [45].

In a phase IIb pilot study of abatacept, 20 patients with DM (n = 9) or PM (n = 11) with refractory disease were enrolled in a randomized treatment delayed-start trial to receive either immediate active treatment with intravenous abatacept or a 3 month delayed-start [46]. Eight/19 patients included in the analyses achieved the definition of improvement (DOI) at 6 months. At 3 months, five (50%) patients responded after active treatment but only one (11%) patient in the delayed treatment arm met the DOI. Overall, abatacept resulted in lower disease activity in nearly half of the enrolled patients. In patients with repeat muscle biopsies, an increased frequency of $Foxp3^+$ Tregs suggested a positive effect of treatment in muscle tissue.

Phase III clinical trials are currently ongoing to assess the efficacy and potential role of abatacept in refractory IIM and IIM-ILD.

## Sifalimumab

There is growing evidence that type I interferon (IFN alpha/beta)-mediated innate immunity may be implicated in the pathogenesis of IIM [47–49]. In a study of 56 patients with adult or juvenile DM (using peripheral blood samples and clinical data), the type I IFN gene and chemokine signature and serum levels of IL-6 correlated with each other and with IIM disease activity [50].

A phase 1b multicenter, randomized, double-blind, controlled, clinical trial assessed sifalimumab, an anti-IFNa monoclonal antibody, in PM and DM [51]. There was suppression of the IFN signature in peripheral blood and muscle tissue (66% and 47%, respectively) which correlated with clinical improvement in patients received sifalimumab. Subjects with $\geq$ 15% improvement in the MMT had greater neutralization of the IFN signature in both peripheral blood and muscle than those with $<$ 15% improvement. These favorable results have led to the initiation of other clinical trials targeting IFN, particularly in DM.

## Ruxolitinib

Janus kinase/signal transducers and activators of transcription pathway inhibition have been reported to mitigate IFN signaling, which is thought to contribute to disease pathogenesis in DM as outlined above. Ruxolitinib, a Janus kinase (JAK) inhibitor, was recently reported to be effective for the treatment of refractory DM [52] in a 72-year-old woman refractory to multiple immunosuppressive agents and IVIg after being diagnosed with a JAK2 mutation-associated myeloproliferative neoplasm. Ruxolitinib monotherapy led to rapid

and significant improvement of DM symptoms with prolonged remission at 12 months.

## Tofacitinib

In a recent series including four subjects with refractory DM who received tofacitinib after failure of several immunosuppressive and immunomodulatory agents, JAK inhibition with tofacitinib resulted in significant improvement in cutaneous and extra-cutaneous manifestations [53]. Four cases of refractory DM have previously been reported to be responsive to tofacitinib [54]. More recently, in the first prospective, open-label clinical trial of tofacitinib in 10 subjects with DM, JAK inhibition with tofacitinib demonstrated strong clinical efficacy as measured by validated myositis response criteria [55]. Another brief report noted a case of refractory PM responding well to tofacitinib [56]. In a recent retrospective study of nine refractory and one new-onset patients with juvenile DM treated with ruxolitinib (n = 7) or baricitinib (n = 3), JAK inhibition led to clinically inactive disease [57].

Japanese investigators reported the possible efficacy of tofacitinib as a rescue option for patients with high-risk amyopathic dermatomyositis-ILD after failure of conventional treatment [58]. In a recent single-center, open-label clinical study of tofacitinib in patients with early-stage anti-MDA5− positive ILD in China, glucocorticoid combined with tofacitinib (5 mg twice daily) led to significant improvement in survival 6 months after the onset of ILD as compared to conventional treatment [59]. The ferritin level, FVC, DLCO, and findings on high-resolution CT were also considerably improved in the tofacitinib group.

## Apremilast

A recent report noted improvement after apremilast, an oral phosphodiesterase 4 inhibitor, in a woman with refractory DM leading to marked skin improvement and complete resolution of scalp pruritus [60]. A recent 12-week phase 1b trial of apremilast in five Japanese patients with refractory DM rashes reported two patient withdrawals and three evaluable female patients [61]. A 39% improvement in the cutaneous dermatomyositis disease area and severity index total activity score at week 12 was observed in all three patients. Further study is warranted to evaluate the efficacy and safety of apremilast in refractory cutaneous DM or potentially earlier in the therapeutic algorithm for DM.

## Anti-tumor necrosis factor (anti-TNF) agents

In a randomized, double-blind, placebo-controlled trial including 12 subjects with active refractory DM or PM, infliximab therapy was well tolerated and deemed to be beneficial for a subset of patients [62]. In general, anti-TNF therapy is not routinely used in IIM as its efficacy is unclear and the risk for inducing PM and DM has been previously noted [35−38]. Anecdotally, anti-TNF agents may be helpful for the management of inflammatory arthropathy in myositis patients.

## Others

Lenabasum is a rationally-designed preferential cannabinoid receptor type 2 agonist that mitigates innate immune responses leading to a reduction in tissue inflammation and fibrotic processes. In an open-label extension of a phase 2 study of lenabasum in refractory skin-predominant dermatomyositis, the CDASI activity score showed improvement [63]. The final results of this Phase 3 study, which did not meet the primary endpoint, have not yet been published.

A phase 2 randomized, controlled multicenter study has been initiated to evaluate the efficacy and safety of KZR-616, selective inhibitor of the immunoproteasome, in the treatment of patients with active PM or DM.

A phase 3 study is underway to evaluate the efficacy and safety of IgPro20 (subcutaneous immunoglobulin, hizentra) in adults with DM.

## Conclusions

The treatment of myositis and MA-ILD patients who experience disease recurrences during or after conventional therapy or those failing to demonstrate a complete response can be challenging. Over the past decade, there have been several small series and a limited number of clinical trials assessing the potential use of novel biologic agents in IIM. While the efficacy data is limited, the biological plausibility of several agents and encouraging results from case series and smaller clinical trials is nonetheless end results, encouraging. Certainly, further research is required to fully assess the role of biologics such as tocilizumab (anti-IL6), abatacept (inhibition of T cell co-stimulation), sifalimumab (anti-IFNα), ruxolitinib/tofacitinib (JAK inhibitors), apremilast (phosphodiesterase 4 inhibitor), and KZR-616 (selective inhibitor of the immunoproteasome).

## Conflict of interest statement

Clinical trial support: Genentech, Bristol Myers Squibb, CSL Behring, Argenx, Janssen, Kezar, Octapharma
Advisory Board: Pfizer, Teva

## References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. * Oddis CV, Reed AM, Aggarwal R, *et al.*: **Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial**. *Arthritis Rheum* 2013, **65**:314−324.

The largest randomized, double-blind, placebo-phase trial of rituximab in adult and pediatric myositis patients. Although there were no significant differences in the 2 treatment arms for the primary and secondary end points, 83% of adult and juvenile myositis patients with refractory disease met the definition of improvement (DOI).

2. Bunch TW, Worthington JW, Combs JJ, Ilstrup DM, Engel AG: **Azathioprine with prednisone for polymyositis. A controlled, clinical trial**. *Ann Intern Med* 1980, **92**:365–369.

3. Dalakas MC, Illa I, Dambrosia JM, *et al.*: **A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis**. *N Engl J Med* 1993, **329**:1993–2000.

4. Miller FW, Leitman SF, Cronin ME, *et al.*: **Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis**. *N Engl J Med* 1992, **326**:1380–1384.

5. Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senécal JL: **Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients**. *Medicine (Baltim)* 2005, **84**:231–249.

6. Koenig M, Fritzler MJ, Targoff IN, Troyanov Y, Senécal JL: **Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes**. *Arthritis Res Ther* 2007, **9**:R78.

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

8. Oddis CV, Rider LG, Reed AMR, *et al.*: **International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies**. *Arthritis Rheum* 2005, **52**:2607–2615.

9. Isenberg DA, Allen E, Farewell V, *et al.*: **International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease**. *Rheumatology (Oxford)* 2004, **43**:49–54.

10. Aggarwal R, Rider LG, Ruperto N, Bayat N, Erman B, Feldman BM, Huber A, Oddis CV, Lundberg I, Amato AA, Cooper RG, Chinoy H, Dastmalchi M, Fiorentino D, Isenberg D, Katz JD, Mammen A, de Visser M, Ytterberg SR, Katalin D, Villa L, Rinaldi M, Rockette H, Lachenbruch P, Miller F, Vencovsky J: **A consensus hybrid definition using a conjoint analysis is proposed as response criteria for minimal and moderate improvement in adult polymyositis and dermatomyositis clinical trials**. *Arthritis Rheum* Oct 2014, **64**(10 Suppl).

11. Mahler EA, Blom M, Voermans NC, van Engelen BG, van Riel PL, Vonk MC: **Rituximab treatment in patients with refractory inflammatory myopathies**. *Rheumatology (Oxford)* 2011, **50**:2206–2213.

12. Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L: **Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series**. *Arthritis Care Res* 2010, **62**:1328–1334.

13. Brulhart L, Waldburger JM, Gabay C: **Rituximab in the treatment of antisynthetase syndrome**. *Ann Rheum Dis* 2006, **65**:974–975.

14. Lambotte O, Kotb R, Maigne G, Blanc FX, Goujard C, Delfraissy JF: **Efficacy of rituximab in refractory polymyositis**. *J Rheumatol* 2005, **32**:1369–1370.

15. Arlet JB, Dimitri D, Pagnoux C, *et al.*: **Marked efficacy of a therapeutic strategy associating prednisone and plasma exchange followed by rituximab in two patients with refractory myopathy associated with antibodies to the signal recognition particle (SRP)**. *Neuromuscul Disord* 2006, **16**:334–336.

16. Levine TD: **Rituximab in the treatment of dermatomyositis: an open-label pilot study**. *Arthritis Rheum* 2005, **52**:601–607.

17. Mok CC, Ho LY, To CH: **Rituximab for refractory polymyositis: an open-label prospective study**. *J Rheumatol* 2007, **34**:1864–1868.

18. Chung L, Genovese MC, Fiorentino DF: **A pilot trial of rituximab in the treatment of patients with dermatomyositis**. *Arch Dermatol* 2007, **143**:763–767.

19. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, Miller FW, Rider LG, Harris-Love MO, Levesque MC, , RIM Study Group, Oddis CV: **Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis**. *Arthritis Rheumatol* 2014 Mar, **66**:740–749.

20. Aggarwal R, Loganathan P, Koontz D, Qi Z, Reed AM, Oddis CV: **Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab**. *Rheumatology* 2017 Feb, **56**:247–254.

21. Keir GJ, Maher TM, Ming D, *et al.*: **Rituximab in severe, treatment-refractory interstitial lung disease**. *Respirology* 2014, **19**(3):353–359.

22. Andersson H, Sem M, Lund MB, *et al.*: **Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease**. *Rheumatology (Oxford)* 2015, **54**(8):1420–1428.

23. Allenbach Y, Guiguet M, Rigolet A, Marie I, Hachulla E, Drouot L, Jouen F, Jacquot S, Mariampillai K, Musset L, Grenier P, Devilliers H, Hij A, Boyer O, Herson S, Benveniste O: **Efficacy of rituximab in refractory inflammatory myopathies associated with anti- synthetase auto-antibodies: an open-label, phase II trial**. *PLoS One* 2015 Nov 5, **10**, e0133702.

24. Bauhammer J, Blank N, Max R, Lorenz HM, Wagner U, Krause D, Fiehn C: **Rituximab in the treatment of Jo1 antibody-associated antisynthetase syndrome: anti-Ro52 positivity as a marker for severity and treatment response**. *J Rheumatol* 2016 Aug, **43**:1566–1574.

25. Ge Y, Li S, Tian X, He L, Lu X, Wang G: **Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis responds to rituximab therapy**. *Clin Rheumatol* 2021 Jun, **40**:2311–2317.

26. Yen TH, Tseng CW, Wang KL, Fu PK: **Combination therapy with rituximab, tofacitinib and pirfenidone in a patient with rapid progressive interstitial lung disease (RP-ILD) due to MDA5 antibody-associated dermatomyositis: a case report**. *Medicina (Kaunas)* 2021 Dec 13, **57**:1358.

27. Mazeda C, Cunha R, Ferreira PG, Barcelos A, Aguiar R: **Myopathy associated with anti-signal recognition particle antibodies with pulmonary involvement and response to rituximab**. *Rheumatol Int* 2021 Jun 4, https://doi.org/10.1007/s00296-021-04904-5. Epub ahead of print.

28. Cherin P, Pelletier S, Teixeira A, *et al.*: **Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients**. *Arthritis Rheum* 2002, **46**:467–474.

29. Danieli MG, Pettinari L, Moretti R, Logullo F, Gabrielli A: **Subcutaneous immunoglobulin in polymyositis and dermatomyositis: a novel application**. *Autoimmun Rev* 2011, **10**:144–149.

30. Miyasaka N, Hara M, Koike T, Saito E, Yamada M, Tanaka Y, GB-0998 Study Group: **Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial**. *Mod Rheumatol* 2012 Jun, **22**:382–393.

31. Suzuki Y, Hayakawa H, Miwa S, *et al.*: **Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis**. *Lung* 2009, **187**:201–206.

32. Bakewell CJ, Raghu G: **Polymyositis associated with severe interstitial lung disease: remission after three doses of IV immunoglobulin**. *Chest* 2011, **139**:441–443.

33. Suzuki Y, Hayakawa H, Miwa S, *et al.*: **Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis**. *Lung* 2009, **187**:201–206.

34. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT: **Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology**. *Neurology* 2012, **78**: 1009–1015.

35. ** Aggarwal R, Charles-Schoeman C, Schessl J, Dimachkie MM, Beckmann I, Levine T: **Prospective, double-blind, randomized, placebo-controlled phase III study evaluating efficacy and safety of octagam 10% in patients with dermatomyositis ("ProDERM Study")**. *Medicine (Baltim)* 2021 Jan 8, **100**, e23677.

The ProDERM (Progress in DERMatomyositis) study evaluated the efficacy, safety and long-term tolerability of IVIg (Octagam 10%) in patients with DM in a randomized, placebo-controlled, double-blind, Phase III study. The positive results of the trial led to the approval of this agent by the U.S. Food and Drug Administration (FDA) for the treatment of adult dermatomyositis.

36. Narazaki M, Hagihara K, Shima Y: **Therapeutic effect of tocilizumab on two patients with polymyositis**. *Rheumatology* 2011, **50**:1344–1346.

37. Kondo M, Murakawa Y, Matsumura T, *et al.*: **A case of overlap syndrome successfully treated with tocilizumab: a hopeful treatment strategy for refractory dermatomyositis?** *Rheumatology* 2014, **53**:1907–1908.

38. * Zhang X, Zhou S, Wu C, Li M, Wang Q, Zhao Y, Zeng X: **Tocilizumab for refractory rapidly progressive interstitial lung disease related to anti-MDA5-positive dermatomyositis**. *Rheumatology* 2021 Jul 1, **60**:e227–e228.

A report of a 43-year-old Chinese man with anti-MDA5 and anti-Ro52-positive DM presented with classic skin rashes, symmetric proximal muscle weak and progressive dyspnea. Rescue IV methylprednisolone pulse therapy and addition of tocilizumab resulted in recovery and normalization of the ILD.

39. Li S, Li W, Jiang W, He L, Peng Q, Wang G, Lu X: **The efficacy of tocilizumab in the treatment of patients with refractory immune-mediated necrotizing myopathies: an open-label pilot study**. *Front Pharmacol* 2021 Mar 16, **12**:635654.

40. Murata K, Dalakas MC: **Expression of the costimulatory molecule BB-1, the ligands CTLA-4 and CD28, and their mRNA in inflammatory myopathies**. *Am J Pathol* 1999, **155**: 453–460.

41. Nagaraju K, Raben N, Villalba ML, *et al.*: **Costimulatory markers in muscle of patients with idiopathic inflammatory myopathies and in cultured muscle cells**. *Clin Immunol* 1999, **92**: 161–169.

42. Musuruana JL, Cavallasca JA: **Abatacept for treatment of refractory polymyositis**. *Joint Bone Spine* 2011, **78**:431–432.

43. Arabshahi B, Silverman RA, Jones OY, Rider LG: **Abatacept and sodium thiosulfate for treatment of recalcitrant juvenile dermatomyositis complicated by ulceration and calcinosis**. *J Pediatr* 2012, **160**:520–522.

44. Maeshima K, Kiyonaga Y, Imada C, *et al.*: **Successful treatment of refractory anti-signal recognition particle myopathy using abatacept**. *Rheumatology* 2014, **53**:379–380.

45. Kerola AM, Kauppi MJ: **Abatacept as a successful therapy for myositis—a case-based review**. *Clin Rheumatol* 2015, **34**: 609–612.

46. Tjärnlund A, Tang Q, Wick C, Dastmalchi M, Mann H, Tomasová Studýnková J, Chura R, Gullick NJ, Salerno R, Rönnelid J, Alexanderson H, Lindroos E, Aggarwal R, Gordon P, Vencovsky J, Lundberg IE: **Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial**. *Ann Rheum Dis* 2018 Jan, **77**(1): 55–62, https://doi.org/10.1136/annrheumdis-2017-211751.

47. Greenberg SA, Pinkus JL, Pinkus GS, *et al.*: **Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis**. *Ann Neurol* 2005, **57**:664–678.

48. Walsh RJ, Kong SW, Yao Y, *et al.*: **Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis**. *Arthritis Rheum* 2007, **56**:3784–3792.

49. Baechler EC, Bauer JW, Slattery CA, et al. An interferon signature in the peripheral Blo6d of dermatomyositis patients is associated with disease activity. Mol Med.

50. Bilgic H, Ytterberg SR, Amin S, *et al.*: **Interleukin-6 and type I interferon-regulated genes and chemokines mark disease activity in dermatomyositis**. *Arthritis Rheum* 2009, **60**: 3436–3446.

51. Higgs BW, Zhu W, Morehouse C, *et al.*: **A phase 1b clinical trial evaluating sifalimumab, an anti-IFN-α monoclonal antibody, shows target neutralisation of a type I IFN signature in blood of dermatomyositis and polymyositis patients**. *Ann Rheum Dis* 2014, **73**:256–262.

52. Hornung T, Janzen V, Heidgen FJ, Wolf D, Bieber T, Wenzel J: **Remission of recalcitrant dermatomyositis treated with ruxolitinib**. *N Engl J Med* 2014 Dec 25, **371**:2537–2538.

53. * Moghadam-Kia S, Charlton D, Aggarwal R, Oddis CV: **Management of refractory cutaneous dermatomyositis: potential role of Janus kinase inhibition with tofacitinib**. *Rheumatology* 2019 Jun 1, **58**:1011–1015.

A series of four subjects with refractory DM who received tofaticinib after failure of several immunosuppressive and immunomodulatory agents. All four subjects responded well to tofacitinib with significant improvement in cutaneous and extra-cutaneous manifestations.

54. Kurtzman DJ, Wright NA, Lin J, Femia AN, Merola JF, Patel M, *et al.*: **Tofacitinib citrate for refractory cutaneous dermatomyositis: an alternative treatment**. *JAMA Dermatol* 2016, **152**: 944–945.

55. * Paik JJ, Casciola-Rosen L, Shin JY, Albayda J, Tiniakou E, Leung DG, Gutierrez-Alamillo L, Perin J, Florea L, Antonescu C, Leung SG, Purwin G, Koenig A, Christopher-Stine L: **Study of tofacitinib in refractory dermatomyositis: an open-label pilot study of ten patients**. *Arthritis Rheumatol* 2021 May, **73**: 858–865.

A recent 12-week phase 1b trial of apremilast in five Japanese patients with refractory DM rashes reported two patient withdrawals and three evaluable female patients. A 39% improvement in the Cutaneous Dermatomyositis Disease Area and Severity Index total activity score at week 12 was observed in all three patients.

56. Babaoglu H, Varan O, Atas N, Satis H, Salman R, Tufan A: **Tofacitinib for the treatment of refractory polymyositis**. *J Clin Rheumatol* 2019 Dec, **25**:e141–e142.

57. Le Voyer T, Gitiaux C, Authier FJ, Bodemer C, Melki I, Quartier P, Aeschlimann F, Isapof A, Herbeuval JP, Bondet V, Charuel JL, Frémond ML, Duffy D, Rodero MP, Bader-Meunier B: **JAK inhibitors are effective in a subset of patients with juvenile dermatomyositis: a monocentric retrospective study**. *Rheumatology* 2021 Dec 1, **60**:5801–5808.

58. Kurasawa K, Arai S, Namiki Y, Tanaka A, Takamura Y, Owada T, Arima M, Maezawa R: **Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis**. *Rheumatology* 2018 Dec 1, **57**:2114–2119.

59. Chen Z, Wang X, Ye S: **Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease**. *N Engl J Med* 2019 Jul 18, **381**:291–293.

60. * Charlton D, Moghadam-Kia S, Smith K, Aggarwal R, English 3rd JC, Oddis CV: **Refractory cutaneous dermatomyositis with severe scalp pruritus responsive to apremilast**. *J Clin Rheumatol* 2021 Dec 1, **27**:S561–S562.

A case of a patient with refractory dermatomyositis with severe scalp pruritus treated with apremilast who demonstrated significant improvement in her skin disease and complete resolution of scalp pruritus.

61. * Konishi R, Tanaka R, Inoue S, Ichimura Y, Nomura T, Okiyama N: **Evaluation of apremilast, an oral phosphodiesterase 4 inhibitor, for refractory cutaneous dermatomyositis: a phase 1b clinical trial**. *J Dermatol* 2022 Jan, **49**:118–123.
This is a phase 1b single-arm, clinical trial of a 12-week course of oral apremilast in five Japanese patients with refractory cutaneous dermatomyositis. A 39% improvement in the Cutaneous Dermatomyositis Disease Area and Severity Index total activity score at week 12 was observed in all three patients.

62. Schiffenbauer A, Garg M, Castro C, Pokrovnichka A, Joe G, Shrader J, Cabalar IV, Faghihi-Kashani S, Harris-Love MO, Plotz PH, Miller FW, Gourley M: **A randomized, double-blind, placebo-controlled trial of infliximab in refractory polymyositis and dermatomyositis**. *Semin Arthritis Rheum* 2018 Jun, **47**:858–864.

63. Werth V, Pearson D, Owaka J, Feng R, Concha JS, Patel B, Hejazi E, Cornwall C, Constantine S, Dgetluck N, White B: **Safety and efficacy of lenabasum in an open-label extension of a phase 2 study of lenabasum in refractory skin-predominant dermatomyositis (DM) subjects**. *Ann Rheum Dis* 2019, **78**:199-200.