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Modern Therapies for Idiopathic Inflammatory Myopathies (IIMs): Role of Biologics

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Abstract

Despite the lack of placebo-controlled trials, glucocorticoids are considered the mainstay of initial treatment for idiopathic inflammatory myopathy (IIMs) and myositis-associated ILD (MA-ILD). Glucocorticoid-sparing agents are often given concomitantly with other immunosuppressive agents, particularly in patients with moderate or severe disease. As treatment of refractory cases of idiopathic inflammatory myopathies has been challenging, there is growing interest in evaluating newer therapies including biologics that target various pathways involved in the pathogenesis of IIMs. In a large clinical trial of rituximab in adult and juvenile myositis, the primary outcome was not met, but the definition of improvement was met by most of this refractory group of myositis patients. Rituximab use was also associated with a significant glucocorticoid-sparing effect. Intravenous immune globulin (IVIg) can be used for refractory IIMs or those with severe dysphagia or concomitant infections. Anti-tumor necrosis factor (anti-TNF) utility in IIMs is generally limited by previous negative studies along with recent reports suggesting their potential for inducing myositis. Further research is required to assess the role of new therapies such as tocilizumab (anti-IL6), ACTH gel, sifalimumab (anti-IFNα), and abatacept (inhibition of T cell co-stimulation) given their biological plausibility and encouraging small case series results. Other potential novel therapies include alemtuzumab (a humanized monoclonal antibody which binds CD52 on B and T lymphocytes), fingolimod (a sphingosine 1-phosphate receptor modulator that traps T lymphocytes in the lymphoid organs), eculizumab, and basiliximab. The future investigations in IIMs will depend on well-designed controlled clinical trials using validated consensus core set measures and improvements in myositis classification schemes based on serologic and histopathologic features.

Keywords

Idiopathic inflammatory myopathy; Myositis; Polymyositis; Dermatomyositis; Treatment; Biologic agents

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Introduction

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic rheumatic diseases that include adult polymyositis (PM), adult dermatomyositis (DM), juvenile myositis (juvenile DM and juvenile PM), myositis associated with other connective tissue diseases or cancer, and inclusion body myositis (IBM). The treatment of IIMs has been challenging without standard therapeutic guidelines. The reasons include the rarity of IIMs, their heterogeneous clinical phenotypes, and the small number of randomized, double-blind controlled clinical trials [1–4].

Traditional treatment includes glucocorticoids and conventional immunosuppressive or immunomodulatory agents such as methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, and intravenous immune globulin (IVIg). As treatment of refractory disease has been difficult, there is growing interest in evaluating novel therapies including newer biologics that target various pathways implicated in the pathogenesis of myositis. Novel schemes for classification of IIMs based on serologic and histopathologic features may also enhance the design of clinical trials and provide guidelines for enrolling subjects [5, 6]. In the past, the measurement of outcomes in myositis clinical trials was based on non-standardized assessment of muscle strength and function. However, over the past several years, consensus core set measures (CSMs) have been introduced to assess myositis disease activity and damage. In particular, two international groups, the International Myositis Assessment and Clinical Studies Group (IMACS) and the Pediatric Rheumatology International Trials Organization (PRINTO), have defined and validated consensus outcome measures for adult and pediatric populations [7–9]. These CSMs along with active international initiatives to develop both data- and consensus-driven response criteria will assist in studying novel therapies in a more rigorous fashion [10]. In this review, we will update the use of biologic therapies for PM and DM [Table 1].

Rituximab

Rituximab, a B cell-depleting agent, is a monoclonal antibody directed against the CD20 antigen on B lymphocytes. The use of rituximab in refractory IIMs has been reported in several small case reports and case series [11–18]. In one study, 13 patients with refractory IIMs were treated with two doses of rituximab, 1000 intravenously, within a 2-week interval and followed for a median of 27 months [11]. The median creatine kinase (CK) and lactate dehydrogenase (LDH) levels dropped significantly compared with baseline, while muscle strength measured by handheld dynamometry increased by 22 % after 24 months. Secondary outcomes including global assessment of general health and health-related quality of life also improved. In another case series, six of eight patients with severe necrotizing myopathy with anti-signal recognition particles (anti-SRP) autoantibody positivity refractory to standard immunosuppressive therapy demonstrated improved muscle strength and/or reduction in CK levels as early as 2 months after rituximab therapy [12]. Three patients had a sustained response for 12–18 months after the initial rituximab dose which was significantly steroid sparing in all patients.

In a small, open-label, uncontrolled, pilot trial of rituximab (four weekly IV doses) in six treatment-resistant DM patients, all patients demonstrated major clinical improvement in muscle strength and rash [13]. Another small open-label trial of rituximab in four patients with refractory polymyositis was associated with return of full muscle strength and significant decline in CK level [14]. However, in another open-label trial of rituximab therapy in eight adult patients with DM, skin disease (skin scores based on Dermatomyositis Skin Severity Index) and CK levels did not significantly change from those at baseline and only three patients showed modest improvement in muscle strength [15].

In the largest randomized, double-blind, controlled trial of rituximab in IIMs, the Rituximab in Myositis (RIM) trial, 195 patients (75 PM, 72 DM, and 48 JDM; all refractory to glucocorticoid therapy and at least one immunosuppressive agent) were randomized to receive two 1 g rituximab infusions either at baseline or 8 weeks later [1]. Entry criteria included fairly significant muscle weakness (not required in the JDM patients) and ≥2 additional abnormal consensus CSMs for adults and ≥3 abnormal CSMs with or without muscle weakness for the pediatric population. Glucocorticoid and/or immunosuppressive therapy was allowed at study entry. The primary endpoint was the time to achieve the IMACS definition of improvement (DOI) which was compared between the two groups (rituximab early and rituximab late). Secondary endpoints included the time to achieve ≥20 % improvement in muscle strength and the proportions of patients in the early and late rituximab groups achieving the DOI at week 8 (the time point at which one half the subjects had received B cell-depleting therapy 8 weeks earlier while the other one half of subjects received placebo). 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 % of this refractory group of myositis patients with a median time to achieving the DOI of 20 weeks. Rituximab use 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 retreated with rituximab after a disease flare responded to retreatment as well. Rituximab therapy was generally well-tolerated, and the most common adverse effects were infections. Additional studies 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 to B cell depletion therapy [19].

PM and DM are frequently associated with interstitial lung disease (ILD) which is a major cause of morbidity and mortality in myositis patients [20, 21]. The efficacy data of rituximab therapy specific to myositis-associated ILD is limited to retrospective uncontrolled studies. In a recent retrospective study of 50 patients with severe, progressive ILD (ten with myositis-associated ILD), rituximab therapy was associated with a median improvement in forced vital capacity (FVC) of 6.7 % ($p < 0.01$) and stability of the diffusing capacity of the lung for carbon monoxide (DLCO) (0 % change; $p < 0.01$) in the 6–12-month period after B cell depletion [22]. The best results were observed in patients with myositis-associated ILD as 5 of the 10 (50 %) myositis patients demonstrated an increase in FVC of >10 % and/or DLCO of >15 % compared to 4 out of 22 (18.2 %) patients with other connective tissue diseases ($p = 0.096$). In a more recent retrospective assessment from the Oslo University

Hospital, 24 patients with anti-synthetase syndrome and severe ILD with more than 12-month follow-up (median 52 months) post-rituximab therapy were identified [23]. The median percentage of predicted FVC, forced expiratory volume in 1 s (FEV1), and DLCO increased by 24, 22, and 17 %, respectively, following B cell depletion. High-resolution CT (HRCT) scanning of their lungs (expressed as a percentage of total lung volume involvement) showed a median of 34 % reduction in ILD extent post-rituximab. The MMT8 score also increased post-rituximab, and the CK also significantly dropped with therapy. Combined therapy with another immunosuppressive agent was a weakness of this study as 10 of the 12 patients with acute disease also received cyclophosphamide making it difficult to attribute the improvement to rituximab alone. The best outcome (>30 % improvement in all three PFT parameters) was noted in seven patients with a disease duration <12 months and/or an acute onset/exacerbation of ILD. However, there were seven deaths among the 34 rituximab-treated patients (six with infection), and three subjects had *Pneumocystis* jirovecii pneumonia.

Rituximab is usually administered as two 1 g doses 2 weeks apart, but the interval may vary. There is also no consensus as to the timing of additional courses of B cell depletion therapy, and this choice is generally made on a case-by-case basis. The most common adverse effects of rituximab include infusion-related reactions, cytopenia, and infections. Some suggest periodic monitoring of peripheral B cell flow cytometry to monitor return of CD20-positive B cells. All patients should be screened for hepatitis B prior to the initiation of rituximab therapy. Patients with a history of recovery from prior hepatitis B infection should be monitored closely for clinical and laboratory evidence of hepatitis B virus reactivation during therapy and for 1–2 years after therapy. High-risk patients require hepatitis C screening as well.

Intravenous Immune Globulin

IVIg, an immunomodulatory agent thought to suppress immune-mediated processes, has demonstrated efficacy in a double-blind, controlled trial of 15 patients with refractory DM [3]. In another open-label trial with 35 PM patients, IVIg therapy was associated with a significant clinical improvement in 70 % of the patients, and the efficacy remained stable in half of the patients 3 after discontinuation of the IVIg [24]. An alternative subcutaneous form of IVIg was associated with significant improvement in CK, muscle strength, and quality of life in all patients in a small series of seven patients (four with DM and three with PM) [25]. In this series, IVIg was administered by a programmable pump, and the patient's usual IVIg monthly dose was fractioned 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 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 noticed in both groups [26]. Few case reports have suggested efficacy for IVIg in the treatment of myositis-associated ILD [27, 28]. In one report, a patient with amyopathic dermatomyositis-associated ILD resistant to high-dose corti-costeroid and cyclosporine A responded well to IVIg [27].

The 2012 American Academy of Neurology guidelines support IVIg therapy for refractory DM but report insufficient evidence to support or refute its use in PM [29].

IVIg is usually administered as infusions of 2 g/kg monthly, but the dose or interval can be changed based on the myositis disease severity and treatment responsiveness. IVIg can be used concomitantly with other immunosuppressive drugs. A major advantage of IVIg is that it is safe in the setting of active infections. The high cost of IVIg may influence decisions on its long-term use.

Anti-Tumor Necrosis Factor Agents

Etanercept and infliximab have been used for the treatment of IIMs, but the results have been mixed and their efficacy in myositis is yet to be established.

In a case series of five patients with active DM refractory to steroid and cytotoxic therapy, etanercept at a dose of 25 mg subcutaneously twice a week for at least 3 months led to an exacerbation of DM with worsening muscle weakness, elevation of muscle enzyme levels, and unchanged rash in all patients [30]. After discontinuing etanercept, the combination of methotrexate and azathioprine therapy resulted in improvement of disease. In contrast, a more recent randomized, double-blind, placebo-controlled trial of etanercept (50 mg subcutaneously weekly) for 52 weeks in 16 DM patients showed that etanercept therapy resulted in a significantly longer median time to treatment failure (358 vs. 148 days; $p = 0.0002$) [31]. In addition, the average prednisone dose after week 24 was significantly lower in the etanercept-treated group than in the placebo group (1.2 vs. 29.2 mg/day; $p = 0.02$). However, given the small number of patients in this study and the earlier negative study on etanercept for myositis, etanercept is not routinely used for myositis and further studies are needed to clarify its role in myositis.

A few anecdotal reports suggested that infliximab might be efficacious in myositis [32–34]. However, two patients who initially appeared to respond to infliximab had an exacerbation of their myositis, and resuming infliximab was associated with anaphylaxis and the development of anti-dsDNA autoantibodies [35]. In a larger retrospective series of eight patients with refractory DM or PM, infliximab therapy was associated with improved motor strength and decreased fatigue but only a partial drop in serum CK [36]. In a more recent pilot study of 13 patients with refractory myositis, four infliximab infusions (5 mg/kg body weight) over 14 weeks was ineffective with no patient showing improvement in their muscle strength [37]. An unpublished randomized placebo-controlled trial of infliximab in myositis also failed to demonstrate efficacy [38]. A multicenter, open-label, placebo-controlled trial of infliximab combined with weekly methotrexate in patients with PM or DM was terminated prematurely because of a low inclusion rate and high dropout due to disease progression and the occurrence of infusion reactions [39].

In general, anti-tumor necrosis factor (anti-TNF) utility in IIMs is limited by negative studies as well as recent reports suggesting their potential for *inducing* autoimmune diseases including PM and DM [40–43].

Tocilizumab

Since the approval of tocilizumab, an anatagonist of the interleukin-6 (IL-6) receptor, for rheumatoid arthritis, there has been growing interest in assessing the potential efficacy of this biologic agent in other systemic rheumatic diseases.

Mononuclear inflammatory cells in IIMs and other inflammatory surrogates at least partially implicate the production of pro-inflammatory cytokines such as IL-6 which is overexpressed in the serum of patients with inflammatory myopathy [44, 45]. While cytokine expression in the muscle tissue of patients with IIMs is dominated by IL-1alpha, IL-1beta, TGF beta1–3, and the type I interferon signature, IL-6 is also observed [46].

In the first report of tocilizumab therapy in inflammatory myopathy, two patients with refractory PM demonstrated improvement in the serum CK level and MRI of their thigh muscles [47]. The first patient was a 40-year-old male with PM and proximal muscle weakness, CK elevation, a myopathic EMG, and anti-Jo-1 autoantibody positivity. Other immunosuppressive agents failed, but tocilizumab at 8 mg/kg initially followed by every 4-week administration resulted in a decline of the serum CK level and prednisolone tapering from 20 to 6 mg/day. There were no adverse events except for a mild elevation of serum low-density lipoprotein (LDL). The second patient was a 31-year-old male with Jo-1-positive PM, a CK of 7962 U/l and repeated flares with the inability to taper prednisolone below 12.5 mg/day. After tocilizumab IV infusions at 8 mg/kg every 4 weeks (later decreased to every 3 weeks) combined with prednisolone 12.5 mg per day and methotrexate, his disease stabilized with normalization of the CK and resolution of abnormal MRI findings of the thighs. No adverse events were reported during tocilizumab therapy.

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, initially responded to high-dose prednisolone therapy but then had worsening of muscle weakness and CK elevation [48]. Trials of cyclosporine, IV cyclophosphamide, IVIg, and tacrolimus were ineffective or partially effective with later development of inflammatory arthritis and anti-CCP positivity. The patient did not respond to methotrexate and adalimumab, but tocilizumab resulted in resolution of skin symptoms, improvement in arthritis, and gradual improvement in the muscle weakness and CK elevation allowing glucocorticoid tapering.

An investigator-initiated, multi-center, randomized, double-blind, controlled trial has begun to assess the efficacy of this agent in refractory adult PM and DM with the University of Pittsburgh as coordinating center (clinicaltrials.gov, NCT02043548).

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that recognizes the cell surface glycoprotein CD52 on B and T lymphocytes, monocytes, and natural killer cells (NK cells), interfering with T cell signaling leading to depletion of both B and T cells.

A single course of alemtuzumab (120 mg over 4 days) resulted in rapid improvement in a 48-year-old woman with PM, ILD (NSIP), pulmonary artery hypertension, and anti-Jo-1 autoantibody positivity refractory to many other immunosuppressive agents [49]. Prednisolone was tapered to 10 mg daily despite an infusion-related reaction consisting of fever, rigors, and bronchospasm. Unfortunately, there was no improvement in her respiratory function following alemtuzumab and sildenafil therapy, and the patient died 1 year later. Further investigations are warranted to verify the effectiveness of alemtuzumab in myositis especially given its marked immunosuppressive properties.

Abatacept

The costimulatory molecules, CD28 and CTLA-4, are upregulated in the muscle tissue of PM and DM patients [50, 51]. Abatacept use was associated with a favorable outcome in a report of refractory PM [52], while a recalcitrant JDM patient with ulcerative skin disease and progressive calcinosis also improved [53]. In another Japanese case report, abatacept was successful in the treatment of refractory anti-signal recognition particle (anti-SRP) myositis [54]. In a more recent report, a patient with severe myositis in overlap with rheumatoid arthritis, peripheral vasculitis, and interstitial lung disease, who had been refractory to many conventional and biologic therapies, responded well to abatacept with good control of the myositis [55]. An ongoing clinical trial (ARTEMIS) is attempting to further investigate the efficacy of abatacept and its potential role in the treatment of refractory myositis.

Safalimumab

There is accumulated evidence that type I interferon (IFN alpha/beta)-mediated innate immunity may be involved in the pathogenesis of myositis. In a study of 67 patients with DM, PM, and other myopathies, clusters of genes known to be induced by IFN-alpha/beta were highly overexpressed in DM patients (n =14) compared to controls [56]. Immunohistochemistry for the IFN-alpha/beta inducible protein MxA (a “downstream” effect of IFN) showed dense tissue staining further implicating type I interferon-inducible genes in the pathogenesis of myositis. A follow-up study from the same investigative group showed similar findings of over-expression of type I IFN genes with IFI27, IFI44L, RSAD2, and IFI44 being the most upregulated genes [57].

Another study also demonstrated a striking IFN signature with increased levels of IFN-regulated cytokines in DM serum samples, both of which also correlated with disease activity [58]. Similarly, using peripheral blood samples and clinical data from 56 patients with adult and juvenile DM, both elevated type 1 IFN-regulated transcripts and IL-6 correlated with each other and with myositis disease activity [59].

A recent phase 1b randomized, double-blinded, controlled, multicenter clinical trial evaluated sifalimumab, an anti-IFNa monoclonal antibody, in PM and DM [60]. Sifalimumab treatment was associated with suppression of the IFN signature in blood and muscle tissue which correlated with clinical improvement.

Conclusion

Conventional treatment regimens for IIMs include glucocorticoids and traditional immunosuppressive or immunomodulatory agents. However, the treatment of refractory IIMs can be challenging. In the last decade, there have been several small series and a limited number of clinical trials assessing the potential use of biologic agents in IIMs even though efficacy data remains limited.

Additional well-designed controlled clinical trials are required to assess the role of biologics in myositis and to develop an evidence-based approach to the treatment of refractory IIMs. Novel myositis classification schemes based on serologic and histopathologic features can assist in better characterization of enrolled subjects while emerging, validated consensus core set measures will further assist in assessing myositis disease activity and damage in future trials. Rituximab in particularly is being used for antisynthetase syndrome as well as for myositis-associated interstitial lung disease given encouraging data on these subsets of patients [19, 22]. Further research is required to assess the role of new therapies such as tocilizumab (anti-IL6), ACTH gel, sifalimumab (anti-IFNα), and abatacept (inhibition of T cell co-stimulation) given their biological plausibility and encouraging small case series results. Agents like alemtuzumab (a humanized monoclonal antibody which binds CD52 on B and T lymphocytes), fingolimod (a sphingosine 1-phosphate receptor modulator that traps T lymphocytes in the lymphoid organs), basiliximab (a monoclonal antibody that blocks the interleukin-2 receptor alpha chain on T and B lymphocytes), and eculizumab (which targets C5 and inhibits the cleavage of C5 to C5a and C5b-9) may hold promise but required further investigation in myositis.

References

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(2):314–324. [PubMed: 23124935]
2. Bunch TW, Worthington JW, et al. Azathioprine with prednisone for polymyositis. A controlled, clinical trial. Ann Intern Med. 1980; 92(3):365–369. [PubMed: 6986827]
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(27):1993–2000. [PubMed: 8247075]
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(21):1380–1384. [PubMed: 1472183]
5. Troyanov Y, Targoff IN, Tremblay JL, et al. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. Medicine (Baltimore). 2005; 84(4):231–249. [PubMed: 16010208]
6. Koenig M, Fritzler MJ, Targoff IN, et al. Heterogeneity of autoantibodies in 100 patients with autoimmune myositis: insights into clinical features and outcomes. Arthritis Res Ther. 2007; 9(4):R78. [PubMed: 17688695]
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 AM, et al. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum. 2005; 52(9):2607–2615. [PubMed: 16142757]
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(1):49–54. [PubMed: 12867580]
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 JA. 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. 2014; 64(10 Suppl)
11. Mahler EA, Blom M, Voermans NC, et al. Rituximab treatment in patients with refractory inflammatory myopathies. Rheumatology (Oxford). 2011; 50(12):2206–2213. [PubMed: 21571768]
12. Valiyil R, Casciola-Rosen L, Hong G, et al. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. Arthritis Care Res. 2010; 62(9):1328–1334.
13. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005; 52(2):601–607. [PubMed: 15692974]
14. Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: an open-label prospective study. J Rheumatol. 2007; 34(9):1864–1868. [PubMed: 17722224]
15. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol. 2007; 143(6):763–767. [PubMed: 17576943]
16. Brulhart L, Waldburger JM, Gabay C. Rituximab in the treatment of antisynthetase syndrome. Ann Rheum Dis. 2006; 65(7):974–975. [PubMed: 16769789]
17. Lambotte O, Kotb R, Maigne G, Blanc FX, Goujard C, Delfraissy JF. Efficacy of rituximab in refractory polymyositis. J Rheumatol. 2005; 32(7):1369–1370. [PubMed: 15996082]
18. 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(5):334–336. [PubMed: 16616848]
19. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, Miller FW, Rider LG, Harris-Love MO, Levesque MC, Oddis CV. RIM Study Group. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheumatol. 2014; 66(3):740–749. [PubMed: 24574235]
20. Kalluri M, Oddis CV. Pulmonary manifestations of the idiopathic inflammatory myopathies. Clin Chest Med. 2010; 31:501–512. [PubMed: 20692542]
21. Marie I, Hachulla E, Chérin P, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum. 2002; 47:614–622. [PubMed: 12522835]
22. Keir GJ, Maher TM, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology. 2014; 19:353–359. [PubMed: 24286447]
23. Andersson H, Sem M, Lund MB, Aaløkken TM, Günther A, Walle-Hansen R, Garen T, Molberg Ø. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology (Oxford). 2015; 54:1420–1428. [PubMed: 25740830]
24. 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(2):467–474. [PubMed: 11840450]

25. Danieli MG, Pettinari L, Moretti R, Logullo F, Gabrielli A. Subcutaneous immunoglobulin in polymyositis and dermatomyositis: a novel application. Autoimmun Rev. 2011; 10(3):144–149. [PubMed: 20858553]
26. 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; 22(3):382–393. [PubMed: 21971943]
27. 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. [PubMed: 19387736]
28. Bakewell CJ, Raghu G. Polymyositis associated with severe interstitial lung disease: remission after three doses of IV immunoglobulin. Chest. 2011; 139:441–443. [PubMed: 21285059]
29. 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(13):1009–1015. [PubMed: 22454268]
30. Iannone F, Scioscia C, Falappone PC, et al. Use of etanercept in the treatment of dermatomyositis: a case series. J Rheumatol. 2006; 33(9):1802–1804. [PubMed: 16960940]
31. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol. 2011; 70(3):427–436. [PubMed: 21688301]
32. Hengstman GJ, van den Hoogen FH, Barrera P, et al. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations. Eur Neurol. 2003; 50(1):10–15. [PubMed: 12824706]
33. Selva-O'Callaghan A, Martínez-Costa X, Solans-Laque R, et al. Refractory adult dermatomyositis with pneumatosis cystoides intestinalis treated with infliximab. Rheumatology (Oxford). 2004; 43(9):1196–1197. [PubMed: 15317960]
34. Anandacoomarasamy A, Howe G, Manolios N. Advanced refractory polymyositis responding to infliximab. Rheumatology (Oxford). 2005; 44(4):562–563. [PubMed: 15695299]
35. Hengstman GJ, van den Hoogen FH, van Engelen BG. Treatment of dermatomyositis and polymyositis with anti-tumor necrosis factor-alpha: long-term follow-up. Eur Neurol. 2004; 52(1): 61–63. [PubMed: 15240986]
36. Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients. Ann Rheum Dis. 2006; 65(9):1233–1236. [PubMed: 16476710]
37. Dastmalchi M, Grundtman C, Alexanderson H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. Ann Rheum Dis. 2008; 67(12):1670–1677. [PubMed: 18272672]
38. Coyle K, Pokrovnichka A, French K. A randomized double blind placebo controlled trial of infliximab in patients with polymyositis and dermatomyositis. Arthritis Res. 2008; 58:S293.
39. Hengstman GJ, De Bleecker JL, Feist E. Open-label trial of anti-TNF-alpha in dermato- and polymyositis treated concomitantly with methotrexate. Eur Neurol. 2008; 59(3–4):159–163. [PubMed: 18230873]
40. Riolo G, Towheed TE. Anti-tumor necrosis factor inhibitor therapy-induced dermatomyositis and fasciitis. J Rheumatol. 2012; 39(1):192–194. [PubMed: 22210682]
41. Klein R, Rosenbach M, Kim EJ, et al. Tumor necrosis factor inhibitor-associated dermatomyositis. Arch Dermatol. 2010; 146(7):780–784. [PubMed: 20644041]
42. Ishikawa Y, Yukawa N, Ohmura K, et al. Etanercept-induced anti-Jo-1-antibody-positive polymyositis in a patient with rheumatoid arthritis: a case report and review of the literature. Clin Rheumatol. 2010; 29(5):563–566. [PubMed: 20143116]
43. Brunasso AM, Scocco GL, Massone C. Dermatomyositis during adalimumab therapy for rheumatoid arthritis. J Rheumatol. 2010; 37(7):1549–1550. [PubMed: 20595297]
44. Lepidi H, Frances V, Figarella-Branger D, et al. Local expression of cytokines in idiopathic inflammatory myopathies. Neuropathol Appl Neurobiol. 1998; 24(1):73–79. [PubMed: 9549732]

45. Gabay C, Gay-Croisier F, Roux-Lombard P, et al. Elevated serum levels of interleukin-1 receptor antagonist in polymyositis/ dermatomyositis. A biologic marker of disease activity with a possible role in the lack of acute-phase protein response. Arthritis Rheum. 1994; 37(12):1744–1751. [PubMed: 7986220]
46. Lundberg I, Ulfgren AK, Nyberg P, et al. Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies. Arthritis Rheum. 1997; 40(5):865–874. [PubMed: 9153548]
47. Narazaki M, Hagihara K, Shima Y. Therapeutic effect of tocilizumab on two patients with polymyositis. Rheumatology (Oxford). 2011; 50(7):1344–1346. [PubMed: 21515628]
48. Kondo M, Murakawa Y, Matsumura T, Matsumoto O, Taira M, Moriyama M, Sumita Y, Yamaguchi S. A case of overlap syndrome successfully treated with tocilizumab: a hopeful treatment strategy for refractory dermatomyositis? Rheumatology (Oxford). 2014; 53(10):1907–1908. [PubMed: 24859996]
49. Thompson B, Corris P, Miller JA, et al. Alemtuzumab (Campath-1H) for treatment of refractory polymyositis. J Rheumatol. 2008; 35(10):2080–2082. [PubMed: 18843768]
50. 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(2):453–460. [PubMed: 10433938]
51. Nagaraju K, Raben N, Villalba ML, Danning C, Loeffler LA, Lee E, Tresser N, Abati A, Fetsch P, Plotz PH. Costimulatory markers in muscle of patients with idiopathic inflammatory myopathies and in cultured muscle cells. Clin Immunol. 1999; 92(2):161–169. [PubMed: 10444360]
52. Musuruana JL, Cavallasca JA. Abatacept for treatment of refractory polymyositis. Joint Bone Spine. 2011; 78(4):431–432. [PubMed: 21550833]
53. 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(3):520–522. [PubMed: 22244459]
54. Maeshima K, Kiyonaga Y, Imada C, Iwakura M, Hamasaki H, Haranaka M, Ishii K. Successful treatment of refractory anti-signal recognition particle myopathy using abatacept. Rheumatology (Oxford). 2014; 53(2):379–380. [PubMed: 23920268]
55. Kerola AM, Kauppi MJ. Abatacept as a successful therapy for myositis—a case-based review. Clin Rheumatol. 2015; 34(3):609–612. [PubMed: 24493331]
56. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, Barohn RJ, Saperstein DS, Briemberg HR, Ericsson M, Park P, Amato AA. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann Neurol. 2005; 57(5):664–678. [PubMed: 15852401]
57. Walsh RJ, Kong SW, Yao Y, Jallal B, Kiener PA, Pinkus JL, Beggs AH, Amato AA, Greenberg SA. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. Arthritis Rheum. 2007; 56(11):3784–3792. [PubMed: 17968926]
58. Baechler EC, Bauer JW, Slattery CA, Ortmann WA, Espe KJ, Novitzke J, Ytterberg SR, Gregersen PK, Behrens TW, Reed AM. An interferon signature in the peripheral blood of dermatomyositis patients is associated with disease activity. Mol Med. 2007; 13(1–2):59–68. [PubMed: 17515957]
59. Bilgic H, Ytterberg SR, Amin S, McNallan KT, Wilson JC, Koeuth T, Ellingson S, Newman B, Bauer JW, Peterson EJ, Baechler EC, Reed AM. Interleukin-6 and type I interferon-regulated genes and chemokines mark disease activity in dermatomyositis. Arthritis Rheum. 2009; 60(11): 3436–3446. [PubMed: 19877033]
60. 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(1):256–262. [PubMed: 23434567]

Table 1

Novel agents used in the treatment of inflammatory myopathy

Drug	Dose	Level of evidence for use in inflammatory myopathy
Rituximab	Two 1 g doses 2 weeks apart but the interval may vary	Double-blind (improvement in IMACS definition of improvement) [1]
Etanercept	50 mg subQ weekly	One placebo-controlled trial of etanercept with significantly longer median time to treatment failure [30]
Infliximab	3 10 mg/kg	Retrospective uncontrolled studies for infliximab [31–33]. Utility in IIMs limited by negative studies as well as potential for *inducing* PM and DM [39–42].
Tocilizumab	8 mg/kg every 4 weeks (decreased to every 3 weeks in one case report)	Case reports [46, 47]
Alemtuzumab	Single course of 120 mg over 4 days	One case report [48]
Abatacept	Varying dosage IVor subQ	Ongoing clinical trial (ARTEMIS)
Sifalimumab	0.3, 1, 3, and 10 mg/kg	One phase 1b controlled trial with suppression of the IFN signature in blood and muscle tissue which correlated with clinical improvement [55]
Intravenous immune globulin (IVIg)	Begin at 1–2 g/kg/month over 1–2 days continuing for 3–6 months depending on response	Double-blind, placebo-controlled trial [3, 26]; case reports for myositis ILD