Expert Perspective: Management of Refractory Inflammatory Myopathy

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The idiopathic inflammatory myopathies (IIMs) are chronic disorders characterized by inflammation in skeletal muscle but also in other organs such as the skin, lungs, joints, gastrointestinal tract, and heart. The effect of immunosuppressive treatment varies between individual patients and between organ manifestations within the same individual. Many patients respond poorly to first-line treatment with glucocorticoids and other immunosuppressive agents such as methotrexate or azathioprine, with symptoms persisting in the muscles, skin, and lungs, leading to refractory disease. Management of refractory IIM is a clinical challenge, and a systematic approach is proposed to better understand the lack of treatment response, in order to guide disease management. The first step in the management of refractory IIM is to recognize whether remaining symptoms are caused by persistent inflammation in the affected tissue or whether the symptoms may be attributable to damage preceding inflammation. Thus, a second diagnostic examination is recommended. Second, in particular for patients with remaining muscle weakness, it is important to ascertain whether the diagnosis of myositis is correct or whether another underlying muscle disorder could explain the symptoms. Third, with confirmation of remaining inflammation in the tissues, a strategy to change treatment needs to be undertaken. Few controlled trials are available to guide our treatment strategies. Furthermore, different subgroups of patients may benefit from different therapies, and different organ manifestations may respond to different therapies. In this context, subgrouping of patients with IIM based on autoantibody profile may be helpful, as there are emerging data from open studies and case series to support the notion of a varying treatment response in different autoantibody-defined subgroups of IIM patients.

Clinical challenge

The index patient, a 38-year-old woman, presented with weakness of the proximal leg muscles, elevated creatine kinase (CK) levels (5 times the upper limit of normal), signs of myopathy on electromyogram, and atrophy of the gluteus muscles on magnetic resonance imaging (MRI). A biopsy sample from the thigh muscle showed some fiber size variation and internal nuclei, but otherwise normal histopathology. She was diagnosed as having polymyositis (PM). Despite having received treatment with high-dose glucocorticoids in combination with azathioprine followed by cyclosporine (methotrexate treatment was excluded due to pregnancy planning) and despite a routine of regular physical exercise, the patient’s muscle weakness progressed and she developed atrophy of her hamstring muscles—a refractory myopathy.

Introduction

This review addresses key issues in the management of refractory idiopathic inflammatory myopathies (IIMs), including the following: 1) how to discern whether progressive and remaining symptoms are attributable to persistent inflammatory disease or whether they may be attributable to organ damage from previous inflammation; 2) how to manage remaining symptoms in the absence of signs of active inflammation; 3) when and how to reevaluate the diagnosis of refractory IIM; and 4) treatment options...
for various clinical manifestations due to persistent inflammation refractory to conventional immunosuppressive treatment.

Background

The IIMs, collectively referred to as myositis, constitute a heterogeneous group of disorders, with proximal muscle weakness as a shared clinical manifestation (1). The IIMs are chronic autoimmune conditions, and many patients have extramuscular manifestations—for example, involvement of the skin, joints, lungs, heart, and gastrointestinal tract. This multiorgan feature suggests that the IIMs are systemic inflammatory disorders. Response to treatment with immunosuppressive drugs varies substantially among patients. Some patients have progressive weakness of the skeletal muscle as the predominating or only clinical manifestation, whereas others have persistent skin rash or develop interstitial lung disease (ILD) despite immunosuppressive treatment. A first challenge in the management of refractory IIM cases is to evaluate whether the remaining clinical manifestations are attributable to persistent inflammation or rather could be attributed to the damage caused by previous inflammation or the side effects of treatment.

A second clinical challenge in the management of IIMs is to make the correct diagnosis, as there are several mimicking conditions characterized by muscle inflammation that will not improve with immunosuppressive treatment (2). The IIMs are also heterogeneous conditions in which different subgroups of patients may respond variably to different therapies. The classic subgroups of IIM, comprising PM, dermatomyositis (DM), and inclusion body myositis (IBM), may each respond differently to various therapies. IBM in all cases is generally refractory to all immunosuppressive therapies (IBM cases will not be discussed further herein).

A major scientific breakthrough with important clinical implications is the discovery of the so-called myositis-specific autoantibodies (MSAs) (3). Serum positivity for MSAs is supportive of a diagnosis of IIM. Moreover, presence of MSAs is strongly associated with clinical subphenotypes of IIM. With the identification of MSAs, new subgroups have been identified in which patients are seemingly clinically more homogeneous than the traditional subgroups of IIM patients; these new subgroups include patients with antisynthetase syndrome (ASyS) and patients with immune-mediated necrotizing myopathy (IMNM) (3).

A third major clinical challenge is the selection of treatment for the individual patient. For a patient with IIM with persistent active inflammatory disease, we have several options but we lack evidence to guide us to select the right treatment for the individual patient. Different organ manifestations may respond to different therapies. Placebo-controlled trials are few. During recent years, the beneficial effects of biologic agents and small molecules have been reported in a number of case series, and some of these involve autoantibody-defined subgroups. These reports are encouraging, indicating a possibility that biomarkers for treatment response may be identified (as discussed herein), but controlled trials are needed.

Approach

Active inflammatory disease or damage? Refractory disease with remaining muscle weakness. In the management of IIM in patients whose disease does not improve with conventional immunosuppressive treatment (i.e., a refractory IIM), a first question to address is whether the remaining symptoms or signs could be attributable to persistent inflammatory disease or whether they may be attributable to damage as a result of previous inflammation (Figure 1). One major clinical problem is the remaining muscle weakness in patients with refractory IIM. Other problems could be skin rash, dysphagia, or dyspnea or cough due to ILD.

An overarching goal in the management of the IIMs is to reduce the systemic and local tissue inflammation, in order to relieve symptoms such as weakness and fatigue. Reducing inflammation will also prevent irreversible organ damage. To facilitate management of treatment, an international collaborative group, the International Myositis and Clinical Studies (IMACS) Group, has proposed and validated a tool to assess disease activity in IIM. This 6-item core set tool includes physician’s and patient’s assessments of disease activity on a 10-cm visual analog scale, scores on the Health Assessment Questionnaire (HAQ), a measure of muscle strength (Manual Muscle Testing in 8 muscle groups [MMT-8]), serum levels of 2 muscle enzymes (CK, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, or aldolase), and an extramuscular score (for symptoms and signs in organs other than the muscle) (4). This core set was developed for clinical trials but is also helpful in clinical practice to follow up patients and to guide treatment decisions. However, specific tools may be needed to evaluate certain clinical manifestations, such as remaining muscle weakness or pulmonary symptoms.

To recognize whether refractory muscle weakness is dependent on persistent muscle inflammation or damage, serum levels of muscle enzymes, such as the serum levels of CK, may not be helpful, as these may normalize with glucocorticoid treatment despite ongoing muscle inflammation. MRI of the skeletal muscles is a sensitive tool to assess muscle inflammation, in which a high signal intensity on STIR and fat-suppressed T2-weighted images of skeletal muscle edema may indicate ongoing inflammation (5). However, this is not specific for IIM, as some non-myositis entities, such as some muscle dystrophies, may also demonstrate “inflammation” in muscle tissue.

Another important tool to detect remaining inflammation is repeated muscle biopsy or a combination using MRI and an MRI-guided muscle biopsy (6). A muscle biopsy is important to confirm inflammation and to exclude other causes of persistent weakness,
such as glucocorticoid-induced myopathy or other mimicking conditions, as discussed below.

**Remaining lung symptoms.** For patients with persistent pulmonary symptoms, repeated pulmonary function testing is a helpful tool to monitor treatment. When the results of pulmonary function tests do not improve as expected, repeated high-resolution computed tomography (HRCT) of the lungs may be helpful to decipher active disease from the development of fibrosis.

**Remaining dysphagia.** Dysphagia is another serious manifestation that may persist despite immunosuppressive treatment. Motility in the pharyngeal and esophageal muscles can be investigated by videofluoroscopy, fiberoptic endoscopic evaluation of swallowing, esophageal manometry, or real-time MRI. These techniques can be helpful for identifying the cause and location of the disturbance causing dysphagia, including any disturbance to the pharyngeal muscles or esophagus (7).

**Remaining muscle symptoms without signs of inflammation.** If there is no sign of persistent inflammation on MRI or muscle biopsy nor signs of inflammation in other organ systems, persistent weakness can most likely be attributable to muscle atrophy or replacement of muscle with fat and connective tissue as a consequence of previous inflammation. Another explanation could be persistent muscle weakness due to loss of muscle mass as a consequence of glucocorticoid treatment (8). Muscle pain without other signs of muscle inflammation could be a sign of generalized pain, and should not be subject to more intense immunosuppressive treatment. For these patients, a physical exercise program guided by a physiotherapist is the first-line treatment (Figure 1). Beneficial effects of physical exercise have been well documented both in patients with chronic PM and in patients with chronic DM, and more recently also in patients with IMNM (9,10). Even in patients with IBM, some improvement of muscle strength or delay in progression of muscle weakness has been reported following exercise programs (11). If the patient is receiving steroid treatment, tapering of the dose should be tried. Notably, occasional patients have developed a transient elevation in the serum CK levels after exercise. If this is observed without worsening of muscle strength or other signs of disease activity, it does not require modification of the immunosuppressive treatment nor does it necessitate discontinuation of exercise.

**Refractory disease with persistent inflammation.**

*Is the diagnosis correct?* In a patient with signs of persistent inflammatory muscle disease, an important question to address is whether the diagnosis or subdiagnosis of IIM is correct (Figure 1). For patients without skin rash and a diagnosis of PM, the possibility of IBM, IMNM, or a muscle dystrophy needs to be considered. A careful new clinical examination with muscle strength testing can be helpful, as well as a repeated screen for autoantibodies (both MSAs and myositis-associated
autoantibodies). A repeated muscle biopsy should be considered to confirm inflammation and to exclude signs of IBM, such as rimmed vacuoles, that may not be present in early disease. Analysis could include immunohistochemical staining for p62, supporting an IBM diagnosis, as well as electron microscopy to find inclusions (12). A repeated muscle biopsy is also important to exclude other myopathies that may mimic inflammatory myopathies, such as limb girdle muscular dystrophy, fascioscapulohumoral muscular dystrophy, metabolic myopathies, and mitochondrial myopathies (2). A close collaboration with neurologists and muscle pathologists and discussions during multidisciplinary rounds is highly recommended. In some cases, genetic testing can be helpful to make the correct diagnosis. For patients with DM and persistent active inflammatory disease, an underlying malignancy should be considered and a repeated screening for cancer may be indicated.

**Treatment options for different clinical manifestations due to persistent inflammation refractory to conventional immunosuppressive treatment.** In cases of an inflammatory myopathy with documented persistent active inflammation despite conventional immunosuppressive treatment, and with the possibility of a diagnosis of IBM or other noninflammatory myopathy being ruled out, a change in the immunosuppressive treatment needs to be undertaken (Figure 2). Overall, only a few randomized controlled trials have been performed in patients with IIM, including trials in patients with refractory IIM, and there are no endorsed international guidelines; therefore, treatment recommendations for refractory cases are mostly based on case series, case reports, and expert opinion (Table 1). Furthermore, most available reports of treatment and outcome are limited to the traditional subgroups (PM, DM, and IBM) and there are few reports on patients with ASyS or IMNM.

In a recent review of treatments for IIM, the recommended first-line therapy is glucocorticoids in combination with azathioprine or methotrexate (13). Second-line therapy in refractory cases includes mycophenolate mofetil (MMF), cyclosporine, or tacrolimus or a combination of methotrexate and azathioprine. Third-line therapy includes rituximab, cyclophosphamide, adrenocorticotropic hormone (also referred to as repository corticotropin injection) (14), other biologic agents such as abatacept or tocilizumab, or new experimental therapies such as JAK inhibitors (15–17). In another recent review of treatments for myositis, MMF was suggested as an alternative first-line therapy in combination with glucocorticoids (18). As a second-line treatment, cyclosporine or tacrolimus have been proposed, and as a third-line treatment, experimental therapies such as leflunomide or JAK inhibitors (tofacitinib or baricitinib) have been proposed (18). Notably, in many countries, the availability of these immunosuppressive drugs (e.g., MMF, rituximab, and abatacept) for off-label use in myositis is limited. There are also restrictions on the use of high-dose IVIG as treatment for patients with IIM. Therefore, local guidelines need to be developed according to availability of therapies.

![Figure 2](image_url)

**Figure 2.** Algorithm for treatment of patients with refractory IIM with persistent muscle weakness and signs of inflammation in skeletal muscle despite having received glucocorticoid (GC) plus GC-sparing immunosuppressive treatment. AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil; DM = dermatomyositis; IVIG = intravenous immunoglobulin; RTX = rituximab; ASyS = antisynthetase syndrome; Ab = antibody; anti-SRP = anti-signal recognition particle; anti-HMGCR = anti-hydroxymethylglutaryl-coenzyme A reductase; PEG = percutaneous endoscopic gastrostomy; ACTH = adrenocorticotropic hormone (see Figure 1 for other definitions).
| Study, first author and year (ref.)       | Level of evidence† | Study population; intervention                                                                 | No. of participants | Primary outcome measure                                                                 | Results                                                                                               | Comments                                                                                           |
|-----------------------------------------|-------------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Drug trials                             |                   |                                                                                                |                     |                                                                                        |                                                                                                      |                                                                                                      |
| RIM Oddis 2013 (40)                     | 1b                | Refractory adult PM (n = 76), and adult DM (n = 76) and juvenile DM (n = 48); rituximab up to 1 gm at weeks 0 and 1 (early) or weeks 8 and 9 (late). | 200                 | Time to reach IMACS DOI.                                                                | Arm A reached DOI after 20.2 weeks and arm B reached DOI after 20.0 weeks (P = 0.74).                | International, multicenter, randomized placebo-controlled trial with rituximab during 44 weeks. Primary end point was not reached, but 83% of patients with refractory PM or DM met DOI. |
| RCi Aggarwal 2018 (14)                  | 1b                | Refractory PM or DM; RCI 80 units SC twice weekly for 24 weeks.                               | 11                  | Meet IMACS DOI.                                                                        | Of 10 patients, 7 met DOI at median of 8 weeks. Mean ± SD prednisone dose decrease from baseline to conclusion 18.5 ± 15.7 to 2.3 ± 3.2 mg (P < 0.01). RCI was considered safe and tolerable. | Open-label clinical trial. Muscle strength improved by >10% and physician global score improved by >40%. RCI was considered safe and tolerable. |
| ARTEMIS Tjärnlund 2018 (15)             | 3b                | Refractory PM/DM; abatacept IV for 6 months.                                                  | 20                  | No. of responders according to IMACS DOI at 6 months. Secondary outcome measures were MMT-8 and TIS scores. | Of 19 patients, 8 achieved DOI (2 with DM, 6 with PM). Muscle performance improved based on MMT-8 scores (P < 0.05). | Open-label, phase Ib, delayed-start design with abatacept. Arm A received active treatment from start. Arm B received active treatment from 3 months. TIS at 3 months was median 28.8 (IQR 15–37.5) in arm A vs. median 5.0 (IQR 0–12.5) in arm B (P = 0.03). |
| Tocilizumab Narazaki 2011 (16)          | 4                 | Refractory PM (1 anti-Jo-1+); tocilizumab at 8 mg/kg every 4 weeks for 3–9 months.          | 2                   | Not defined.                                                                            | Clinical improvement based on decrease in serum CK levels, decrease in prednisolone dose, and improved MRI findings. Improvement in the MRC5/CDASI scores and serum IFNa levels (no significance values given). | Case report on the first use of tocilizumab in a patient with PM.                                    |
| JAK inhibitor Ladislau 2018 (17)        | 4                 | Effect of type I IFN in vitro plus refractory DM; treated with ruxolitinib up to 40 mg/day for 3 months. | 4                   | MRC muscle score 5, CDASI scores, serum IFNa levels.                                      |                                                                                                      | Case series and in vitro studies supporting effects on type I IFN in refractory DM.                    |
| Exercise trials                         |                   |                                                                                                |                     |                                                                                        |                                                                                                      |                                                                                                      |
| Alexanderson 2020 (9)                   | 2a                | PM, DM established disease; exercise and resistance training.                                | 8                   | Systematic literature review.                                                            | Aerobic exercise and resistance training can improve muscle strength.                                | Systematic literature review summarizing exercise studies in IIMs.                                   |
| De Souza 2019 (10)                      | 4                 | IMNM (anti-SRP+ or anti-HMGCR); aerobic exercise test, 1RM muscle strength test for 12 weeks. | 8                   | IMACS core set measures, aerobic exercise test, 1RM muscle strength test, STS function test, SF-36 score, VRM of 5, patient preference, maximized VO2, no. of responders based on IMACS core set measures. | Improved aerobic capacity, muscle strength, and STS function.                                       | Open study. No worsening of disease status.                                                          |
| Alemo Munters 2013 (39)                 | 1b                | Established PM, DM; 1-hour endurance exercise 3 times per week for 12 weeks, with 1-year follow-up. | 21                  | Systematic literature review.                                                            | Improved physical function and vitality (P = 0.010 and P = 0.046), maximized VO2 (P = 0.010), reduced disease activity. | Randomized controlled trial. Endurance exercise improves health and may reduce disease activity.      |
| Jørgensen 2018 (11)                     | 1b                | IBM; blood flow–restricted resistance training, 2 times per week for 12 weeks.               | 22                  | Systematic literature review.                                                            | Scores on the physical function domain of the SF-36.                                                | A randomized controlled trial. No significant improvement of muscle strength, but the protocol had a preventive effect on the disease-related decline in leg muscle strength. |

† Burns PB, Rohrich, RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305–10.

* IIMs = idiopathic inflammatory myopathies; RIM = Rituximab in Myositis; PM = polymyositis; DM = dermatomyositis; IMACS = International Myositis Assessment and Clinical Studies (Group); DOI = preliminary definition of improvement; RCI = repository corticotropin injection; SC = subcutaneously; ARTEMIS = Abatacept Treatment in Polymyositis and Dermatomyositis; IV = intravenous; MMT-8 = Manual Muscle Testing in 8 muscle groups; TIS = total improvement score; IQR = interquartile range; CK = creatine kinase; MRI = magnetic resonance imaging; IFN = interferon; MRC = Medical Research Council Scale for Muscle Strength (scale 0–5, with 5 indicating normal); CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; IMNM = immune-mediated necrotizing myopathy; anti-SRP+ = anti–signal recognition particle antibody positive; anti-HMGCR+ = anti–hydroxymethylglutaryl-coenzyme A reductase antibody positive; 1RM = One Repetition Maximum; STS = Sit-to-Stand; SF-36 = 36-item short form general health survey; VRM = voluntary repetition maximum; IBM = inclusion body myositis.
Refractory muscle weakness with persistent inflammation. A multidisciplinary team to manage this often-complicated disease is recommended. Muscle strength and muscle endurance are clinically important outcome measures. Notably, the Functional Index in myositis 2 (FI-2) or its shorter version, FI-3 (19,20), which measures number of repetitions in several muscle groups, is more sensitive than the MMT-8 for the detection of impairment of muscle performance (21,22).

Importantly, measurable effects on muscle performance can take months, and at least 3 months should be allowed to measure objective improvement of muscle performance, although findings from laboratory tests, such as serum levels of CK, may normalize sooner (23). Specifically, in patients with DM, a normalization of the CK level may be seen in conjunction with persistent muscle inflammation, which necessitates a high degree of clinical suspicion and careful monitoring of clinical manifestations. In some patients with IIM, the major refractory clinical manifestation may be extramuscular; management of these specific refractory clinical manifestations are discussed below.

Refractory ILD with persistent inflammation. ILD is a common manifestation in patients with IIM and can be either rapidly or slowly progressive, or even asymptomatic. If the inflammatory process in the lungs cannot be stopped, the manifestation can become life-threatening. Both slowly progressive and rapidly progressive ILD can be refractory to treatment (Figure 3). Treatment of ILD in patients with IIM needs to be initially aggressive. Induction therapy with high-dose glucocorticoids, administered either orally or as intravenous (IV) pulses, in combination with an immunosuppressive drug (azathioprine, MMF, cyclosporine, or tacrolimus) is recommended (13) (Table 2). MMF has increasingly been used for the treatment of other systemic autoimmune diseases and is well tolerated and efficient in the treatment of ILD associated with systemic sclerosis (24). In a retrospective study comparing azathioprine and MMF in patients with ILD and myositis, MMF was equally as effective as azathioprine but with fewer side effects, thereby supporting the notion that MMF can be used as a first-line therapy in this subgroup of patients with IIM (25).

In cases of IIM with refractory ILD, the addition of rituximab or cyclophosphamide or a combination of MMF and tacrolimus are all possible approaches (Figure 3), as proposed in a review by Drs. C. Oddis and R. Aggarwal (13). As a third-line therapy in refractory ILD, abatacept or other new therapies that are being evaluated in ongoing clinical trials can be tried (13). One of the most challenging groups of patients in the disease spectrum of IIM is the subgroup of patients with rapidly progressive ILD (RPILD). These cases are often associated with anti–melanoma differentiation–associated protein 5 (anti-MDA5) autoantibodies (as further discussed below).

In patients with progressive ILD and declining respiratory function, collaboration with pulmonary medicine specialists is recommended to 1) determine the need for oxygen therapy, 2) initiate pulmonary rehabilitation with the aim of improving exercise capacity, dyspnea, and quality of life, and 3) begin early discussions on the patient’s eligibility for lung transplantation.

Antifibrotic therapy (e.g., pirfenidone and nintedanib) has been shown to reduce the decline in lung function in patients with...
### Table 2. Selected studies on the treatment of specific refractory clinical manifestations of IIMs*

| Manifestation, first author and year (ref.) | Level of evidence† | Study population; intervention | No. of participants | Primary outcome measure | Results | Comments |
|--------------------------------------------|-------------------|--------------------------------|---------------------|------------------------|---------|----------|
| ILD Huapaya 2019 (25)                       | 4                 | Myositis-related ILD; AZA or MMF retrospectively over 2–5 years. | 110 | Change in FVC%, DLco%, and prednisone dose. | FVC% improved and prednisolone dose was reduced after 2–5 years in both groups. DLco% improved in AZA group. More AEs in the AZA group. | Retrospective study. AZA vs. MMF effects on FVC%, DLco%, and prednisone dose. |
| Skin rash Dalakas 1993 (29)                | 1b                | Refractory DM; high-dose IVIG at 2 gm/kg body weight per month for 3 months. | 15 | Neurumuscular symptom score | Significant improvement of muscle strength (P < 0.018) and neuromuscular symptoms (P < 0.035). Intragroup changes. | Double-blind, placebo-controlled trial. IVIG was added to immunosuppressive treatment. Also improvement in skin rash and muscle histopathologic features, including increased muscle fiber diameter and number of capillaries. |
| Werth 2018 (31)                            | 1b                | DM skin rash refractory to hydroxychloroquine; lenabasum at 20 mg twice per day, open-label extension study at 4–92 weeks. | 20 | CDASI. Physician global score. Patient global score on VAS. PROMIS-29 scores of physical function, fatigue, pain interference, and anxiety. | Lenabasum was well tolerated. Improvements in the CDASI, physician global, and PROMIS-29 scores. | 28-week open-label extension study with lenabasum, BT101-DM-001 (ClinicalTrials.gov identifier NCT02466243). |
| Paik 2021 (32)                             | 2b                | Refractory DM; open-label 12-week study with tofacitinib at 11 mg daily (extended release form). | 10 | IMACS, DOI using the TIS. Secondary outcome measure, CDASI score. | All 10 patients met the primary outcome measure, of whom 5 showed moderate improvement and 5 showed minimal improvement. CDASI score improved (P = 0.0005). | Open-label study demonstrating efficacy of tofacitinib in refractory DM. |
| Arabshahi 2012 (33)                        | 4                 | Juvenile DM with calcinosis; abatacept at 10 mg/kg with IV and topical sodium thiosulfate. | 1 | CMAS, MMT-8, and C- HAQ scores. | Improvement of CMAS, MMT-8, and C-HAQ scores. Halted progression of calcinosis confirmed with plain radiography. | Case report, abatacept for 6 months. Concomitant pain medication and glucocorticoid treatment was reduced. |
| Wendel 2019 (34)                           | 4                 | Refractory calcinosis in adult DM; tofacitinib at 5 mg twice per day for 28 weeks. | 2 | Reduction of calcifications. | Calcifications were reduced. | Case report. Tofacitinib for 28 weeks. |
| Charlton 2019 (35)                         | 4                 | Adult ADM, refractory skin rash with severe scalp pruritus; apremilast at 30 mg twice per day for 3 months. | 1 | Not defined. | Improved skin rash. Resolution of scalp rash and pruritus. | Case report. |
| Pinal-Fernandez 2019 (36)                  | 4                 | Refractory mechanic's hands in ASyS (anti-Jo-1+). Ustekinumab at 45 mg SC for 3 months. | 1 | Skin changes. | Improvement of skin lesions on hands and of mechanic's hands. | Case report. Ustekinumab added to prednisolone and mycophenolate. Other manifestations remained under control. |
| Dysphagia Marie 2010 (37)                  | 4                 | PW/DM with steroid-resistant esophageal involvement; IVIG at 2 gm/kg body weight monthly for 6 months. | 73 (39 PM, 34 DM) | Esophageal manifestations assessed clinically or by manometry. | 82% resolution of clinical esophageal manifestations. | Retrospective review of medical charts. Median follow-up 32 months (IQR 1–92). |

* ILD = interstitial lung disease; AZA = azathioprine; MMF = mycophenolate mofetil; FVC% = forced vital capacity % predicted; DLco% = diffusion capacity for carbon monoxide % predicted; AEs = adverse events; IVIG = intravenous immunoglobulin; VAS = visual analog scale; PROMIS-29 = patient-reported outcome measures short form; CMAS = Childhood Myositis Assessment Scale; C-HAQ = Childhood Health Assessment Questionnaire; ADM = amyopathic DM; ASyS = antisynthetase syndrome (see Table 1 for other definitions).
† Burns PB, Rohrich, RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128(3):9–10.
Idiopathic pulmonary fibrosis (IPF) (26). Recently, nintedanib was demonstrated to reduce the annual rate of decline in the forced vital capacity (FVC) in patients with SSc-ILD compared to those who received placebo (27). Other large trials evaluating the safety and efficacy of antifibrotic drugs in treating connective tissue disease–associated ILD are ongoing (NIBUILD trial; ClinicalTrials.gov identifier NCT02999178). Notably, ILD in patients with myositis is mainly inflammatory, and pulmonary function may improve with immunosuppressive treatment, in contrast to the observations in patients with IPF.

**Refractory skin rash with persistent inflammation.** For management of refractory skin rash with persistent active inflammation, a close collaboration with a dermatologist is recommended (Table 2). Treatment with hydroxychloroquine can be helpful to diminish skin rash. Notably, hydroxychloroquine may be associated with a paradoxical reaction of exfoliative DM, most notably in patients with anti-SAE-positive DM (28).

In cases of severe, refractory skin rash, high-dose IVIG is an alternative treatment, supported by the findings from a recently reported placebo-controlled trial (29,30). Lenabasum, a cannabinoid, had beneficial effects on refractory skin rash in patients with DM (31), and a placebo-controlled trial is ongoing (ClinicalTrials.gov identifier NCT02466243). Another promising option for the treatment of refractory skin rash is JAK inhibitors (32).

Cutaneous or subcutaneous calcinosis, which is mostly observed in patients with juvenile-onset DM and young adults with DM, is very difficult to treat but should be regarded as a sign of persistent underlying inflammation, and should be considered an indicator for the need to optimize the immunosuppressive treatment. Beneficial effects of abatacept on calcinosis were reported in 1 patient with juvenile DM (33), and tofacitinib was observed to have some beneficial effects in an adult patient with DM (34). Severe pruritus may also be refractory to conventional immunosuppressive treatment. In this regard, anecdotal reports of the beneficial effects of apremilast may be of interest (35), and in patients with ASyS with refractory mechanic’s hands, ustekinumab may be an alternative treatment (36).

**Refractory dysphagia with persistent inflammation.** Dysphagia is common in patients with IIM. It can be life-threatening because of the concomitant development of aspiration pneumonia. In all patients with dysphagia, it is recommended that proton inhibitors be used. Some patients may need a percutaneous gastrostomy to allow adequate supply of nutrition. Cases of severe dysphagia should be managed in collaboration with speech therapists or other experts on dysphagia according to local practice, in order to advise patients on how to minimize the risk of swallowing into the respiratory tract. In most patients, dysphagia improves with conventional immunosuppressive treatment. Alternatively, the beneficial effects of high-dose IVIG (Table 2) in some cases have been reported (37). Persistent dysphagia can be explained by dysmotility of the pharyngeal muscles attributed to low endurance of swallowing musculature. This problem is not likely to respond to any immunosuppressor or surgical treatment of the esophagus. Rather, these patients may benefit from swallowing exercises (38). Severe cases need to be managed together with ear, nose, and throat specialists; in particular, in patients with IBM, dilation of the pharyngeal muscles may sometimes relieve swallowing problems to facilitate nutrition.

The immunosuppressive treatment needs to be combined with active physical exercise to recover muscle strength and to promote development of lost skeletal muscle mass (39,39). Exercise should be recommended at the time of diagnosis, to diminish damage from treatment with glucocorticoids and from disuse of muscles; however, the exercises should be individually adapted to the level of disease activity, extent of muscle weakness, and internal organ damage, as well as the pain and fatigue levels in each patient (Table 2). It is recommended that exercise should be initiated by a trained physical therapist with regular follow-up. Exercise should be started on a low intensity, and gradually increased over time based on clinical improvement (9). Evidence supporting exercise as a disease-modifying treatment with antinflammatory effects in patients with established, low-activity PM or DM has emerged (9,39). Patients need long-term follow-up by physical therapists and occupational therapists, since it has been shown that patients are limited in muscle endurance, aerobic capacity, and hand function, and also experience high levels of pain and fatigue and low quality of life despite low disease activity (21,22).

**Treatment options for refractory inflammatory disease in autoantibody-defined subgroups of IIM.** Most reports on the treatment of refractory IIM include patients classified as having either PM or DM. During recent years, some studies have indicated that patients with MSAs may respond variably (either better or worse) to different immunosuppressive drugs (Table 3). The fact that the presence of certain autoantibodies may be predictive of the treatment response was suggested by the findings from the Rituximab in Myositis (RIM) trial, which failed to reach its primary end point—the time to achieve a preestablished definition of improvement (40). However, a post hoc analysis revealed that adult patients with anti–Jo-1 or anti–Mi-2 autoantibodies were more likely to improve following treatment with rituximab, as assessed using the 6-item core set of disease activity measures, when compared to patients who were negative for these autoantibodies (41).

**Antisynthetase syndrome.** The largest autoantibody-defined subgroup is patients with ASyS. This is also the autoantibody-defined subgroup of patients with IIM for whom most of the reported series on management of refractory cases is available. The anti–Jo-1 autoantibody is the most prevalent antisynthetase autoantibody, present in ~20–30% of patients with IIM, whereas the other antisynthetase autoantibodies are each present in <5% of patients with IIM. ASyS is characterized by multiorgan involvement, including myositis, ILD, arthritis, mechanic’s hands, and
| Autoantibody subset, first author and year (ref.) | Level of evidence† | Study population | No. of participants | Primary outcome measure | Results | Comments |
|-----------------|-------------------|------------------|--------------------|------------------------|---------|----------|
| Antisynthetase Aggarwal RIM trial 2014 (41) | 1b | Refractory adult PM (n = 76), adult DM (n = 76), and juvenile DM (n = 48). Placebo-controlled trial with rituximab (2 arms for rituximab, early or late). Post-hoc analysis of the RIM trial (39). | 195 | Time to reach IMACS DOI at 2 consecutive time points. | Presence of an antisynthetase antibody, primarily anti-Jo-1 (HR 3.08, \( P < 0.01 \)), anti-Mi-2 (HR 2.5, \( P < 0.01 \)), or other autoantibody (HR 1.4, \( P = 0.14 \)) was predictive of a shorter time to improvement compared to the absence of autoantibodies. | Multivariable model. Predictors of response in the RIM trial were presence of anti-Mi-2 and antisynthetase autoantibodies, juvenile DM subgroup (HR 2.45, \( P = 0.01 \)), and low physician global score of damage (HR 2.32, \( P = 0.02 \)). |
| Allenbach 2015 (42) | 2b | Refractory ASyS (9 anti-Jo-1+, 1 anti-PL7+). Rituximab was administered at 1 gm on days 1 and 15, and month 6. | 12 | Increase of at least 2 Kendall points (of 10) in >2 muscle groups on the MMT-10 at month 12. | Of 10 patients, 2 met the primary end point, and 4 experienced improvement in the FVC% by 10%. | Open-label phase II trial for 12 months. |
| Andersson 2015 (43) | 4 | ASyS with severe ILD (19 anti-Jo-1+, 3 anti-PL7+, 2 anti-PL-12+, 18 anti-SSA+) of 24 with refractory disease. | 24 | Pulmonary function tests. Extent of ILD on HRCT. MMT-8 scores. | FVC% improved 24% (\( P < 0.018 \)) and DLco% improved 17% (\( P < 0.025 \)) after a median of 52 months. Reduced extent of ILD on HRCT by 34% (\( P < 0.001 \)). Improved MMT-8 scores (\( P < 0.05 \)). Mortality rate 21%. | Retrospective case series with >12 months follow-up. Rituximab effect on ILD. Best effect seen on PFT was in patients with symptoms for <12 months. Most cases had received another immunosuppressive treatment. High mortality rate due to infections. |
| Doyle 2018 (44) | 4 | ASyS with ILD (16 anti-Jo-1+, 3 anti-PL7+, 6 anti-PL-12+). Of 25 patients, 21 had refractory disease. Rituximab was administered for 12 months. | 25 | Pulmonary function. ILD severity on HRCT and concurrent GC dosing. | CT scan (n = 8 evaluated) showed stable or improved findings in 88% of patients. FVC% remained stable or improved >10% in 79% of patients (n = 19 evaluated). After 3 years' follow-up (n = 7), FVC% improved by 21% (\( P = 0.016 \)). | Retrospective case series (3 cases excluded due to either early death [n = 1] or lung transplantation [n = 2]). |
| Anti-MDA5 Tsuji 2020 (45) | 2b | Anti-MDA5+ patients with DM/ADM and ILD. Triple combination with high-dose GCs, tacrolimus, and IV CYC. Plasmapheresis added if worsening occurred. Historical control group received step-up treatment. | 29 | 6-month survival. Secondary outcome measures of 12-month survival, AEs, changes in laboratory data. | 89% survival at 6 months vs. 33% in historical control group (\( P < 0.0001 \)). Plasmapheresis added for treatment of refractory cases (31%). | Open prospective study in Asian patients with new-onset disease compared to historical control group. CMV reactivation in 85%, more common in triple combination group (\( P = 0.0015 \)). |
| Autoantibody subset, first author and year (ref.) | Level of evidence† | Study population | No. of participants | Primary outcome measure | Results | Comments |
|-----------------------------------------------|-------------------|------------------|---------------------|------------------------|---------|----------|
| Romero-Bueno 2020 (46)                        | 3                 | Consensus paper. Scientific review. | – | – | Recommendations for treatment of anti-MDA5+ patients with DM and RPILD using combination therapy with immunosuppressive drugs. | Literature review, expert consensus. |
| Huang 2019 (47)                               | 4                 | Anti-MDA5+ Canadian patients with DM. All had ILD, 8 of 21 had RPILD. | 21 | Description of clinical features and treatment. | Overall mortality was 23.8%, and 5 of 8 patients with RPILD died; 3 received ECMO and lung transplantation and survived. | Case series. Retrospective chart review. |
| Chen 2019 (48)                                | 2b                | Anti-MDA5+ patients with new-onset ADM and ILD for <3 months and FVC% ≥50% for >18 years. | 18 | Survival at 6 months. | 6-month survival 18 of 18 patients vs. 25 historical controls (78%) (P = 0.04), FVC% improved (P < 0.001), and DLco% improved (P < 0.007). | Single-center open-label trial in patients with new-onset ADM and ILD. AEs in the tofacitinib group were low grade. |

Anti-SRP/anti-HMGCR
Valiyil 2010 (50)

| Anti-SRP+ patients with refractory disease. Rituximab administered at 1 gm/m², repeated after 2 weeks. | 4 | Manual muscle strength according to the MRC scale. Serum CK levels. | Of 8 patients, 4 had improved muscle strength and 2 had decreased serum CK levels. | Retrospective case series. |

Mammen 2015 (51)

| New statin treatment triggered anti-HMGCR+ myopathy and diabetes. High-dose IVIG administered at 2 gm/kg body weight per month. | 4 | Serum CK levels. Muscle strength quantitative dynamometry. | Improved muscle strength in 3 of 3 patients (arm abduction from 3.5 to 6.2 kg), hip flexor strength increased, serum CK levels declined from mean ± SD 4,919 ± 3,523 to 1,125 ± 1,101 IU per liter. Improvement was seen after 1.5–3 months. | Case series. High-dose IVIG as first-line monotherapy. |

* HR = hazard ratio; ASyS = antisynthetase syndrome; FVC% = forced vital capacity % predicted; ILD = interstitial lung disease; HRCT = high-resolution computed tomography; DLco% = diffusion capacity for carbon monoxide % predicted; PFT = pulmonary function test; GCs = glucocorticoids; anti-MDA5 = anti-melanoma differentiation-associated protein 5; ADM = amyopathic DM; CYC = cyclophosphamide; AEs = adverse events; CMV = cytomegalovirus; RPILD = rapidly progressive ILD; ECMO = extracorporeal membrane oxygenation; MRC = Medical Research Council Scale for Muscle Strength; IVIG = intravenous immunoglobulin (see Table 1 for other definitions).† Burns PB, Rohrich, RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305–10.
Raynaud’s phenomenon (3). Some patients experience all manifestations simultaneously, whereas others only have 1 or 2 of the manifestations. Moreover, 1 manifestation can respond to treatment whereas another may be refractory. During recent years, several reports, in addition to those from the RIM trial, have indicated that patients with antisynthetase autoantibodies who do not respond to conventional immunosuppressive treatment may improve with anti-CD20 therapy. Thus, patients with antisynthetase autoantibodies who have refractory muscle symptoms or arthritis may show improvement with rituximab treatment (42). Furthermore, refractory ILD associated with antisynthetase autoantibodies may respond to treatment with rituximab, as suggested by the findings from retrospective studies and case series in which improved results on pulmonary function tests and improved HRCT scores of the lungs have been reported (42–44). In these cases, adding or switching to rituximab may be an alternative treatment.

**Anti-MDA5 antibody–positive ILD.** A specific clinical challenge is the treatment of RPILD, often seen in patients with anti-MDA5 autoantibodies in whom mild or no clinical muscle symptoms are present (known as clinical amyopathic DM [CADM]). This condition can be life-threatening and extremely refractory to immunosuppressive treatment with high-dose glucocorticoids in combination with cyclophosphamide or rituximab. Experts from Asia, where this severe phenotype of IIM seems to be more common than among White populations, recommend administering induction therapy to patients with RPILD using a triple combination of high-dose IV glucocorticoids in combination with IV cyclophosphamide and a calcineurin inhibitor, tacrolimus, which they found in an open-label prospective trial to reduce the frequency of mortality as compared to that in historical controls (45). Recently, investigators from Spain recommended treatment strategies for anti-MDA5–positive RPILD based on a literature review and consensus discussions. These recommendations are to start with combination therapy, including glucocorticoids and a calcineurin inhibitor with or without IV cyclophosphamide (46). In refractory cases, adding an immunosuppressive drug (cyclophosphamide, MMF, rituximab, basiliximab, or tofacitinib) to the current therapy or even switching from one immunosuppressive agent to the other should be considered (46). For refractory, severe RPILD, a combination of rituximab and cyclophosphamide could be another option, although this is potentially associated with a high risk of infections (13). As a third step, adding high-dose IVIG, plasmapheresis, or polymyxin B has been suggested as rescue therapies (46). Even with aggressive immunosuppressive treatment, the mortality rate is considerable in this subgroup of patients with IIM, and in refractory cases, planning for lung transplantation should be initiated. Extracorporeal membrane oxygenation may be indicated while waiting for transplantation (47).

**JAK inhibitors have emerged as a new potential effective treatment in anti-MDA5–positive RPILD.** In an open-label trial of patients with anti-MDA5–positive amyopathic DM and ILD, tofacitinib in combination with glucocorticoids was used in the induction phase, before the devastating ILD had developed (48). Excellent results were reported with this treatment, resulting in 100% survival at 6 months and improved pulmonary function test results, notably in patients with a disease duration of <3 months and FVC of >50% (48). In these cases, the rate of adverse events was low. These results need to be confirmed in larger studies, preferably placebo-controlled trials, both in refractory cases and in new-onset cases. Anti–signal recognition particle (anti-SRP) antibody–positive and anti–hydroxymethylglutaryl-coenzyme A reductase (anti-HMGCR) antibody–positive myopathy. Another subgroup of patients with IIM, the so-called IMNM, is associated with anti-SRP or anti-HMGCR autoantibodies (3). Patients with anti-SRP or anti-HMGCR autoantibodies frequently develop severe muscle impairment refractory to conventional immunosuppressive treatment such as glucocorticoids and methotrexate. These patients often have signs of muscle fiber necrosis with sparse or no detectable inflammation on muscle biopsy. Treatment recommendations for this subgroup have been promulgated from a European Neuromuscular Centre workshop (49). For treatment of refractory disease in patients with anti-SRP autoantibodies, the addition of rituximab infusions may improve muscle strength (50). For patients with anti-HMGCR autoantibodies, high-dose IVIG may have a dramatic effect, even as a monotherapy (51).

**Discussion**

The index patient in our clinical challenge case was started on treatment with azathioprine in combination with prednisolone, and when no improvement was noted, cyclosporine was added, but still no clinical improvement of muscle strength was seen, despite regular exercise. In this case, my approach would have been to switch the patient to methotrexate, but only if she had not expressed a wish to become pregnant. Moreover, as long as it was used as a third-line therapy, I would have suggested treatment with MMF. The patient had persistently elevated serum CK levels, but she did not have any signs of skin, lung, heart, or joint involvement and she had no problems with swallowing. Her symptoms were restricted to her proximal leg muscles. Her autoantibody profile, as determined using the LineBlot test, yielded negative results. As a next step of treatment, I could have proposed abatacept or rituximab, but at that time, there was some hesitancy because it was unclear whether the diagnosis was correct. The patient still wanted to become pregnant and she felt she could tolerate her muscle weakness.

We performed a second diagnostic evaluation on the patient. An MRI of the thigh muscles showed progressive fatty infiltration of the hamstrings and adductor muscles in the thighs. A second muscle biopsy showed occasional regenerating muscle fibers but no degenerating or necrotic fibers and no signs of
inflammation. All immunsuppressive treatment was stopped. The patient was referred back to the neurologist and a new evaluation for a suspected limb girdle muscular dystrophy and Pompe’s disease was performed, but genetic testing failed to reveal any known mutations. The patient moved to another city and was referred to the local neurologist and continued with a tentative diagnosis of a muscular dystrophy.

Ten years thereafter, a new subset of IIM was described: IMNM associated with anti-HMGCR autoantibodies (52,53). In the first case report, a remarkable association with previous statin use was observed. This observation was followed up by reports of young people with a refractory IIM who were positive for anti-HMGCR autoantibodies but had not received statins (52). This prompted us to analyze anti-HMGCR autoantibodies in the stored serum from our patient, and it turned out to be strongly positive. The patient and her neurologist were notified and again her diagnosis was changed to anti-HMGCR–positive IIM or IMNM, although her muscle biopsy never displayed any fiber necrosis. Based on her serum positivity for HMGCR autoantibodies, she was started on treatment with high-dose IVIG as suggested by some case reports, and for the first time since her diagnosis of IIM she experienced improvement of muscle strength, which could be confirmed by muscle strength testing (53).

Identification of MSAs has helped us to define new subgroups of IIM, since some MSA-positive patients seem to benefit from different therapeutic approaches, such as anti-HMGCR–positive patients with refractory disease who may experience an excellent response to high-dose IVIG. However, we still need more clinical trials to guide our management of the disease in patients with IIM. We need to develop treatment regimens that would prevent the development of a refractory disease. One current limitation is that we lack biomarkers that could guide us when making decisions on treatment for the individual with newly diagnosed IIM. We need studies that aim to address which patients with IIM are likely to respond to conventional immunsuppressive treatment and, indeed, also whether there are differences in response between subgroups of patients to different conventional immunsuppressive agents such as methotrexate, azathioprine, MMF, or calcineurin inhibitors.

To address these questions, we need to study large cohorts with longitudinal data. One approach could be observational studies of well-characterized patients who are followed up using validated outcome measures in longitudinal registries. There is also a clear unmet need to develop therapies for patients who are refractory to conventional immunsuppressive treatments, as is obvious from the discussion above. Here again, one way forward could be to employ an observational study design and use data from longitudinally followed up patients in large multicenter, international registries. From these studies we may even be able to compare the effect of different therapies by making use of restrictions in availability of drugs in different countries. One possibility for improving the effects of treatment could be a treat-to-target approach, as is now adopted in several rheumatic diseases. For this, we need to define and agree upon targets and apply these in studies of patients with IIM, and importantly, we need different targets depending on the dominating clinical manifestation in the individual patient. In ongoing and new clinical trials, subgroup analyses according to autoantibody profile should be conducted, as this may give us important information on biomarkers to guide treatment response for autoantibody-defined subgroups of IIM.

Several studies on treatment effects over recent years and as discussed herein have been focused on patients in different autoantibody-defined subgroups. These observations from clinical practice have brought new information that is helpful in the management of patients with refractory disease. Still, almost 40% of the patients with myositis are seronegative and they are excluded from the autoantibody-defined cohorts. The seronegative group with IIM is a specific diagnostic challenge, in particular patients without DM-associated skin rash. Patients with signs of inflammatory myopathy without skin rash have, by different classification criteria, been classified as having PM. With the discovery of the antisynthetase autoantibodies as well as of the antibodies associated with IMNM (anti-SRP and anti-HMGCR antibodies), the PM subgroup has decreased as patients have been classified into these new subgroups. However, we still have patients that can be classified as having PM. These patients need to be carefully followed up, because the clinical manifestations of PM can resemble IBM, adult-onset muscle dystrophies, or metabolic myopathies. We still need to explore the seronegative subgroup of patients with IIM to identify biomarkers for treatment response and improvement. In addition to refractory muscle weakness, 2 additional clinical manifestations that are challenging to treat are refractory ILD with development of pulmonary fibrosis and calcinosis of the skin. The new antifibrotic treatments could potentially be effective in patients with refractory myositis-associated ILD, but we need clinical trials to guide treatment decisions. Likewise, we need systematic studies on calcinosis to understand its pathophysiology, with the aim of enhancing development of new therapies for this condition.

With the currently available immunsuppressive treatments, in combination with exercise, many patients improve partially, but few recover former muscle strength, and very few go into remission and can stop immunsuppressive treatment. Most patients with IIM experience a chronic disease course with high morbidity and mortality. Therefore, there is a high unmet need for new therapeutic options. In order to develop these therapies, we need to acquire a better understanding of the molecular pathophysiology leading to this autoimmune disorder and to the development of a chronic disease. For this approach, subgrouping patients according to autoantibody profile may be one way forward. IIM is a rare disorder, and the subgroups are even smaller. Thus, international collaborations with large cohorts of well-characterized patients with follow-up data in registries are needed as a standardized approach to improving the management of refractory IIM.
AUTHOR CONTRIBUTIONS

Dr. Lundberg drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Lundberg IE, de Visser M, Werth VP. Classification of myositis [review]. Nat Rev Rheumatol 2018;14:269–78.
2. Chinoy H, Lilleker JB. Pitfalls in the diagnosis of myositis [review]. Best Pract Res Clin Rheumatol 2020;34:101-186.
3. Mchugh NJ, Tansley SL. Autoantibodies in myositis [review]. Nat Rev Rheumatol 2018;14:290–302.
4. Isenben DA, Allen E, Farewell V, Ehrenstein MR, Hanna MG, Lundberg IE, et al. development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 2004;43:49–54.
5. Maurer B, Walker UA. Role of MRI in diagnosis and management of idiopathic inflammatory myopathies. Curr Rheumatol Rep 2015;17:67.
6. Lampa J, Nennesmo I, Einarssdottr H, Lundberg I. MRI guided muscle biopsy confirmed polymyositis diagnosis in a patient with interstitial lung disease. Ann Rheum Dis 2001;60:423–6.
7. Zeng R, Schmidt J. Impact and management of dysphagia in inflammatory myopathies. Curr Rheumatol Rep 2020;22:74.
8. Navata T, Kubo M, Nomura T, Oishi K, Shragarni K, Ikegami T, et al. Change in muscle volume after steroid therapy in patients with myositis assessed using cross-sectional computed tomography. BMC Musculoskeleton Disord 2018;19:93.
9. Alexanderson H, Bostrom C. Exercise therapy in patients with idiopathic inflammatory myopathies and systemic lupus erythematosus: a systematic literature review. Best Pract Res Clin Rheumatol 2020;34:101547.
10. De Souza JM, de Oliveira DS, Perin LA, Misse RG, Dos Santos AM, Gualano BL, et al. Feasibility, safety and efficacy of exercise training in immune-mediated necrotizing myopathies: a quasi-experimental prospective study. Clin Exp Rheumatol 2019;37:235–41.
11. Jorgensen AN, Aagaard P, Frandsen U, Boye E, Diederichsen LP. Blood-flow restricted resistance training in patients with sporadic inclusion body myositis: a randomized controlled trial. Scand J Rheumatol 2018;47:400–9.
12. Hilton-Jones D, Brady S. Diagnostic criteria for inclusion body myositis. J Intern Med 2016;280:52–62.
13. Oddis CV, Aggarwal R. Treatment in myositis [review]. Nat Rev Rheumatol 2018;14:279–89.
14. Aggarwal R, Marder G, Koonetz DC, Nandkumar P, Qi Z, Oddis CV. Efficacy and safety of adrenocorticotropic hormone gel in refractory dermatomyositis and polymyositis. Ann Rheum Dis 2018;77:720–7.
15. Tjarnlund A, Tang Q, Wick C, Dastmalchi M, Dani L, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. Ann Rheum Dis 2018;77:55–62.
16. Narazaki M, Hagiha K, Shima Y, Ogata A, Kishimoto T, Tanaka T. Therapeutic effect of tocilizumab on two patients with polymyositis. Rheumatology (Oxford) 2011;50:1344–6.
17. Ladislau L, Suárez-Calvet X, Toquet S, Landon-Cardinal O, Amelini D, Depp M, et al. JAK inhibitor improves type I interferon induced damage: proof of concept in dermatomyositis. Brain 2018;141:1609–21.
18. Glabitsz S, Zeng R, Schmidt J. New insights into the treatment of myositis [review]. Ther Adv Musculoskeletal Dis 2020;12:1759720X19886494.
19. Alexanderson H, Bromlan L, Tollbäck A, Josefson A, Lundberg IE, Stenström CH. Functional Index 2: validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum 2006;15:114–22.
20. Ernesto FC, Chong C, Crowson CS, Kermani TA, Mhurcheartagh ON, Alexanderson H. Functional Index 3: a valid and reliable functional outcome assessment measure in dermatomyositis and polymyositis patients. J Rheumatol 2021;48:94–100.
21. Alexanderson H, Regardt M, Ottosson C, Muters LA, Dastmalchi M, Dani L, et al. Muscle strength and muscle endurance during the first year of treatment of polymyositis and dermatomyositis: a prospective study. J Rheumatol 2018;45:538–46.
22. Amici DR, Pinal-Fernandez I, Pagkatipunan R, Mearns A, de Lorenzo R, Tiniakou E, et al. Muscle endurance deficits in myositis patients despite normal manual muscle testing scores. Muscle Nerve 2019;59:70–5.
23. Oddis CV, Rider LG, Reed AM, Brunner HI, Koneru B, et al. For the International Myositis Assessment and Clinical Studies Group. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum 2005;52:2607–15.
24. Tashkin DP, Roth MD, Clements PJ, Forst DE, Khamne D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS: II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.
25. Huapaya JA, Silihan L, Pinal-Fernandez I, Casal-Dominguez M, Johnson C, Altayba J, et al. Long-term treatment with azathioprine and mycophenolate mofetil for myositis-related interstitial lung disease. Chest 2019;156:986–906.
26. Richeldi L, Varone F, Bergna M, de Andrade J, Falk J, Hallowell R, et al. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev 2018;27:180074.
27. Dietler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518–28.
28. Wolstencroft PW, Cascolia-Rosen L, Florentino DF. Association between autoantibody phenotype and cutaneous adverse reactions to hydroxychloroquine in dermatomyositis. JAMA Dermatol 2018;154:1199–203.
29. Dalakas MC, Ila I, Darnbroisa JM, Soueidan SA, Steín DP, Otaro C, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993;329:1993–2000.
30. Aggarwal R, Charles-Schoeman C, Schess J, Betts-Csorgo Z, Dimachkie M, Griger Z, et al. Efficacy and safety of Mfg (Octagam 10%) in patients with active dermatomyositis: results of a randomised, double-blind, placebo-controlled phase III trial (ProDERM Study) [abstract]. Arthritis Rheumatol 2020;72 Suppl 10. URL: https://acrabstracts.org/abstract/efficacy-and-safety-of-ivig-octag-am-10-in-patients-with-active-dermatomyositis-results-of-a-randomized-double-blind-placebo-controlled-phase-iii-trial-prode-
31. Werth VP, Patel B, Concha JS, Okawa J, Pearson D, Heizaji E, et al. Safety and efficacy of lenalabasum in refractory skin-predominant dermatomyositis subjects treated on an open-label extension of trial JBT101-DM-001 [abstract]. Arthritis Rheumatol 2018;70 Suppl 10. URL: https://acrabstracts.org/abstract/safety-and-efficacy-of-lenalabasum-in-refractory-skin-predominant-dermatomyositis-subjects-treated-on-an-open-label-extension-of-trial-jbt101-dm-001/.
32. Paik JJ, Cascolia-Rosen L, Shin JY, Altayba J, Tiniakou E, Leung DG, et al. Study of tofacitinib in refractory dermatomyositis: an open label pilot study of 10 patients. Arthritis Rheumatol 2021;73:858–65.
33. 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;160:520–2.

34. Wendel S, Venhoff N, Frye BC, May AM, Agarwal P, Rizzi M, et al. Successful treatment of extensive calcifications and acute pulmonary involvement in dermatomyositis with the janus-kinase inhibitor tofacitinib: a report of two cases. J Autoimmun 2019;100:131–6.

35. Charlton D, Moghadam-Kia S, Smith K, Aggarwal R, English JC III, Oddis CV. Refractory cutaneous dermatomyositis with severe scalp pruritus responsive to apremilast [letter]. J Clin Rheumatol 2019 doi: 10.1097/RHU.0000000000000999. E-pub ahead of print.

36. Pinal-Fernandez I, Kroodsma CT, Mammen AL. Successful treatment of refractory mechanic’s hands with ustekinumab in a patient with the antisynthetase syndrome. Rheumatology (Oxford) 2019;58:1307–8.

37. Marie I, Menard JF, Hatron PY, Hachulla E, Mouthon L, Tiev K, et al. Intravenous immunoglobulins for steroid-refractory esophageal involvement related to polymyositis and dermatomyositis: a series of 73 patients. Arthritis Care Res (Hoboken) 2010;62:1748–55.

38. Azola A, Mulheren R, Lloyd T, Christopher-Stine L, Palmer J, et al. Dysphagia in myositis: a study of the structural and physiologic changes resulting in disordered swallowing. Am J Phys Med Rehabil 2020;99:404–8.

39. Alemo Munters L, Dastmalchi M, Andgren V, Emilson C, Bergegård J, Regardt M, et al. Improvement in health and possible reduction in disease activity using endurance exercise in patients with established polymyositis and dermatomyositis: a multicenter randomized controlled trial with a 1-year open extension followup. Arthritis Care Res (Hoboken) 2013;65:65–68.

40. Oddis CV, Reed AM, Aggarwal R, Rider LG, Ascherman DP, Levesque MC, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013;65:314–24.

41. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, et al. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheumatol 2014;66:740–9.

42. Allenbach Y, Guiguet M, Rigolet A, Marie I, Hachulla E, Drouot L, et al. Efficacy of rituximab in refractory inflammatory myopathies associated with anti-synthetase auto-antibodies: an open-label, phase II trial. PLoS One 2015;10:e0133702.

43. Andersen H, Sorn M, Lund MB, Aalekken TM, Günther A, Waaler-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology (Oxford) 2015;54:1420–8.

44. Doyle TJ, Dhillion N, Madan R, Cabral F, Fletcher EA, Koontz DC, et al. Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: a multicenter retrospective case review. J Rheumatol 2018;45:841–50.

45. Tsuji H, Nakashima R, Hosono Y, Imura Y, Yagita M, Yoshifuji H, et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti–melanoma differentiation-associated gene 5-positive dermatomyositis. Arthritis Rheumatol 2020;72:488–98.

46. Romero-Bueno F, del Campo PD, Trallero-Araguás E, Ruiz-Rodríguez JC, Castellvi I, Rodríguez-Nieto MJ, et al. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. Semin Arthritis Rheum 2020;50:776–90.

47. Huang K, Vinik O, Shojania K, Yeung J, Shupak R, Nimm M, et al. Clinical spectrum and therapeutic strategies in Canadian patients with anti-melanoma differentiation-associated gene 5 (MDA5)-positive dermatomyositis: a case-based review. Rheumatol Int 2019;39:1971–81.

48. Chen Z, Wang X, Ye S. Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease [letter]. N Engl J Med 2019;381:291–3.

49. Allenbach Y, Mammen AL, Benveniste O, Szerzé L, on behalf of the Immune-Mediated Nekrotisierende Myopathien Working Group, 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016. Neuromuscul Disord 2018;28:87–89.

50. 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 (Hoboken) 2010;62:1328–34.

51. Mammen AL, Tiniakou E. Intravenous immune globulin for statin-triggered autoimmune myopathy [letter]. N Engl J Med 2015;373:1680–2.

52. Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL. A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum 2010;62:2757–66.

53. Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011;63:713–21.