Published in final edited form as:

Semin Neurol. 2012 July ; 32(3): 227–236. doi:10.1055/s-0032-1329201.

Idiopathic Inflammatory Myopathies

Mazen M. Dimachkie, M.D.¹ and Richard J. Barohn, M.D.¹

¹Department of Neurology, The University of Kansas Medical Center, Kansas City, Kansas

Abstract

The idiopathic inflammatory myopathies are a group of rare disorders including polymyositis (PM), dermatomyositis (DM), and autoimmune necrotizing myopathies (NMs). The idiopathic inflammatory myopathies share many similarities. They present acutely, subacutely, or chronically with marked proximal and symmetric muscle weakness, except for associated distal and asymmetric weakness in inclusion body myositis. The idiopathic inflammatory myopathies also share a variable degree of creatine kinase (CK) elevation and a nonspecifically abnormal electromyogram demonstrating an irritative myopathy. The muscle pathology demonstrates inflammatory exudates of variable distribution within the muscle fascicle. Despite these similarities, the idiopathic inflammatory myopathies are a heterogeneous group. The overlap syndrome (OS) refers to the association of PM, DM, or NM with connective tissue disease, such as scleroderma or systemic lupus erythematosus. In addition to elevated antinuclear antibodies (ANA), patients with OS may be weaker in the proximal arms than the legs mimicking the pattern seen in some muscular dystrophies. In this review, we focus on DM, PM, and NM and examine current and promising therapies.

Keywords

myositis; polymyositis; dermatomyositis; necrotizing myopathy

The idiopathic inflammatory myopathies are rare sporadic disorders.¹ Their annual incidence, using older diagnostic criteria, is approximately one in 100,000. Except for juvenile dermatomyositis (JDM), the idiopathic inflammatory myopathies are diseases of the adult. They affect more women than men. There is recent controversy around the frequency of polymyositis (PM). In a retrospective study from the Netherlands that originally excluded inclusion body myositis (IBM), necrotizing myopathy (NM) represented 19% of the idiopathic inflammatory myopathies, while dermatomyositis (DM) and nonspecific myositis accounted for 36% and 39% of all idiopathic inflammatory myopathies, respectively.² Polymyositis was less common than expected, accounting for 2% of cases.² However, a PM clinical phenotype was the most common cause of PM pathology in the Mayo Clinic case series.³ Indeed, 27 of 43 cases with PM pathology had clinical features of PM, while 37% had clinical features of IBM, PM pathology, and lacked rimmed vacuoles. The later clinical phenotype is predictive of IBM diagnosis and of poor treatment response. The incidence of DM and PM increased with advancing age and reached a peak at age 50 to 59 years.⁴

Clinical Presentation

Dermatomyositis

Dermatomyositis presents with acute or insidiously progressive, painless, proximal weakness and/or a characteristic skin rash. Patients with acute disease and/or subcutaneous calcifications can have significant pain. Proximal weakness results in difficulty using the arms while elevated over the head and being unable to get up from a deep chair or to climb stairs. This pattern is similar to most other myopathies. Dermatomyositis may result in dysphagia, chewing difficulty, and sometimes dysarthria. Juvenile DM commonly presents after a febrile episode and skin rash. Multisystem involvement is common in JDM.

The characteristic skin rash usually antedates or occurs concurrently with the onset of weakness. The degree of muscle versus skin involvement varies. Amyopathic DM presents with isolated rash and adermatopathic DM with isolated myositis. The DM rash can be quite discrete and evade detection. A heliotrope rash is the typical purplish discoloration of the eyelids and is often associated with periorbital edema. Generalized or limb edema is uncommon. Gottron's papules, an erythematous lichenoid papular pathognomonic scaly rash, appear on the extensor surface of the hands and fingers. Occasionally, the papules are located on the volar aspect and are referred to as inverse Gottron's papules.⁵ A macular erythematous rash may affect the face, neck, and anterior chest ("V-sign"), upper back ("shawl sign"), the extensor surface of the elbows, knuckles, knees, or toes (Gottron's sign). At times, the nail beds have dilated capillary loops with periungual hyperemia. Nailfold capillary density is reduced in JDM and is inversely associated over time with muscle and skin disease activity.⁶ Subcutaneous calcinosis is common in JDM but is uncommon in adults. "Mechanic's hands," thickened and cracked skin on the dorsal and ventral surfaces of the hands, is encountered in patients with the antisynthetase syndrome (arthritis, Raynaud's phenomenon, interstitial lung disease). Cutaneous symptoms, including prominent pruritus, have a significant impact on quality of life.^{7,8}

A working group of international experts has published proposed classification criteria of the idiopathic inflammatory myopathies,⁹ which are currently being validated in an ongoing study. This system is based on clinical criteria, CK elevation, other laboratory criteria, and muscle biopsy criteria. Dermatomyositis is classified as definite, probable, amyopathic and possible DM sine dermatitis.

Polymyositis

Polymyositis is an exclusionary diagnosis in patients who do not have a rash or alternate muscle or nerve disease.¹⁰ Though the existence of PM has been questioned,^{2,11} recent studies confirm its existence as a distinct clinical entity, accounting for 63% of patients with histologic findings of PM.³ Revised classification criteria factor in advances in our understanding of PM immunopathogenesis.¹⁰

Polymyositis is a disease of adults over the age of 20 years and is more common in women.^{10,12,13} As in DM, PM patients have progressive neck flexor and symmetric proximal limb muscle weakness, which typically develops subacutely or insidiously over weeks to months. Myalgias and tenderness are common, but not presenting complaints. Dysphagia occurs in one-third of patients, and mild facial weakness is occasionally present. In patients with an acute quadriparetic presentation, weakness of jaw-opening was noted in 71% of PM/DM cases whereas this was rarely present (4%) in the Guillain-Barré syndrome.¹⁴ Extraocular muscles are spared.

Necrotizing Myopathy

Necrotizing myopathy is an increasingly recognized autoimmune myopathy that has little or no inflammatory infiltrate.⁹ Necrotizing myopathy presents with a subacute progressive proximal muscle weakness without a rash. Weakness generally develops more rapidly than with PM, and in 30% is markedly severe.² There may be associated myalgia and dysphagia. In the Dutch series,² NM occurred in 19% of 165 idiopathic inflammatory myopathy cases with a female-to-male ratio of 2:1. In an Australian case series, the mean age of diagnosis was 57 years for NM (range 19–89 years) and 61% were male.¹⁵ The median CK was 1,941 units per liter (U/L), significantly higher than those with idiopathic inflammatory myopathy.

Paraneoplastic necrotizing myopathy is a rare, rapidly progressive, severe variant that affects adults over the age of 40, frequently with adenocarcinoma. Necrotizing myopathy with perivascular capillaritis affects a similar age group and is associated with subacute weakness, brain infarction due to vasculitis, or connective tissue disease. Signal recognition particle (SRP) autoantibodies affect younger NM patients, women more than men, and typically occur in the fall season. It results in severe or fulminant weakness and cardiac complications including congestive heart failure. Treatment refractory SRP-associated NM cases have been reported in children as young as age 5, with initial misdiagnosis of muscular dystrophy.¹⁶

In predisposed individuals, statin medications may induce an autoimmune NM, which progresses beyond 3 to 6 months after drug discontinuation.¹⁷ The vast majority require immunosuppressive therapy, suggesting an autoimmune mechanism. Statin-induced autoimmune NM (SANAM) affects individuals between 46 and 89 years of age (mean 65.5 years). The onset of SANAM may be delayed up to 10 years following statin initiation. In one-third of cases onset may occur several months (range of 0.5–20 months) after statin discontinuation.

Associated Conditions

There is an increased incidence of interstitial lung disease, autoimmune disorders, cancer, and cardiac disorders in patients with DM, PM, and NM. In JDM, necrotizing vasculitis of the gastrointestinal system may cause bowel ischemia, necrosis, and perforation. It may be associated with a petechial rash or even a muscle infarct. Polyarthritis has been reported in up to 45% of patients with PM at the time of diagnosis.¹⁸ Autoimmune disorders, including scleroderma and mixed connective tissue disease, are frequently associated with NM.

Ten to 25% of adult idiopathic inflammatory myopathy patients have interstitial lung disease manifesting as dyspnea and cough.¹⁹ Interstitial lung disease may occur in JDM and has been reported in 10% of PM cases, with the majority having Jo-1 antibodies.^{20,21} These autoantibodies are more closely associated with DM than with PM.² Interstitial lung disease may affect up to 30% of DM and PM cases.¹⁹ A chronic progressive course is most common, whereas 5% may have an acute presentation. Interstitial lung disease may antecede or follow the diagnosis of PM or DM in one-third of patients.

Although malignancy has been reported in as many as 45% of patients,²² most studies suggest 15%²³ to 25%²⁴ of adult DM patients, especially those older than 40 years, have preexisting, concurrent, or future malignancies. In women, the most common DM-associated malignancy is ovarian cancer,²⁵ and in men it is small cell lung cancer. Treatment of the malignancy, which may present 2 years after the DM onset, improves muscular involvement. Rarely, malignancy has been reported in JDM.²⁶ Although it is not as elevated as in DM, the risk of malignancy is increased in PM and NM when compared with the general population.²⁷

Although cardiac conduction defects and arrhythmias may occur, pericarditis and congestive heart failure are less common. As many as one-third of PM patients may have myocarditis; it manifests primarily as conduction abnormalities and less commonly as congestive heart failure. SRP autoantibodies predict a fulminant form of refractory PM or NM that rapidly progresses over 1 month to severe weakness and may be associated with myocarditis.²⁸ There is an increased of cardiovascular disease in the idiopathic inflammatory myopathies.^{29,30}

Laboratory Studies

Serum creatine kinase (CK) level is increased in the majority of DM patients, with levels ranging up to 50 times the upper limit of normal. In less than 10% of DM, and regardless of severity, the CK level may be normal. In contrast, CK is always elevated in active PM in the range of 5 to 50 times the upper limit of normal and is increased 10 times or more in NM. A decrease or increase in CK level generally correlates with good treatment response or relapse respectively, but the clinical evaluation is more precisely indicative of disease activity than CK.

Screening for malignancy is important in DM but also NM and PM, especially early in the diagnosis. Data on cost effectiveness of cancer screening in DM is limited to retrospective case series. Our approach includes a careful skin examination for melanoma; computed tomography (CT) scan of the chest, abdomen, and pelvis; and in women, a mammogram and pelvic examination; in men, testicular and prostate examinations are indicated. The European Federation of Neurological Societies Task Force recommended that DM patients have CT of the chest/abdomen, pelvic ultrasound and mammography in women, ultrasound of testes in men under 50 years, and colonoscopy in men and women over 50. If primary screening is negative, repeat screening is recommended after 3 to 6 months; thereafter screening is recommended every 6 months for 4 years.³¹

Symptoms of interstitial lung disease should prompt chest imaging and pulmonary function testing, as well as a prompt pulmonary consultation. The most common autoantibody associated with interstitial lung disease is the Jo-1 (histidyl t-RNA synthetase) antibody, occurring in 50% of idiopathic inflammatory myopathy patients with interstitial lung disease (ILD).^{20,21} Besides serial imaging and pulmonary function testing, serum KL-6,³² SP-D, IL-18, and ferritin levels may be useful biomarkers for monitoring ILD activity and severity.³³

Though there are no published prospective studies, current experience suggests that most of the so-called myositis-specific antibodies (MSAs) (Table 1), are predictors of poor treatment response. This is likely to be due to the association with interstitial lung disease. However, these antibodies, which are only present in a minority of DM patients, have an unknown and controversial pathogenetic role. The MSAs include two classes of cytoplasmic antibodies: those directed against Mi-2 and Mas antigens and others targeting translational proteins, such as various tRNA synthetases, the SRP, transcriptional intermediary factor-1 (TIF1; anti-155/140 Ab), and the melanoma differentiation-associated gene-5 (MDA5; anti-CADM140 Ab).³⁴ The Jo-1 antibody is associated with interstitial lung disease, arthritis, Raynaud's phenomenon, and mechanic's hand's,²¹ and is seen in up to 20% of idiopathic inflammatory myopathies.^{20,21} The other antisynthetases (PL-7, EJ, KS, OJ, PL-12) are less common, occurring in fewer than 2 to 3% of idiopathic inflammatory myopathy cases. Antibodies to nuclear matrix protein NXP2, previously known as MJ antibodies, are among the most common MSAs in JDM, but occur in less than 2% of adult DM cases with up to 50% having an associated malignancy.³⁴ Nonsynthetase antibodies to Mi-2, a 240-kd nuclear protein of unknown function, are found in 15 to 30% of DM patients. Mi-2

antibodies are associated with a favorable prognosis.^{21,35} However, it is unknown whether DM cases with Mi-2 antibody respond differently from those without this antibody.

SRP antibodies have been reported in 5 to 8% of PM patients and are more closely associated with NM.³⁶ Patients present in the fall with rapidly progressive and severe proximal weakness that is often steroid resistant.³⁷ Cardiac involvement and ILD are common. An MSA may be present in up to one-third of NM cases. However, SRP antibodies may be nonspecifically positive in patients with alternate muscle diagnosis or no evidence of muscle involvement.³⁸

We routinely obtain Jo-1 antibodies in all idiopathic inflammatory myopathy cases. Because 50% of Jo-1 positive patients either have or will develop ILD, methotrexate should be avoided. Antibodies to SRP should be measured in severe fulminant PM or NM because they predict a rapid course leading to muscle fibrosis and marked cardiac involvement, and thus indicate need for aggressive and swift pharmacotherapy.

More recently, anti-200/100 autoantibodies have been described in a unique subset of patients with myopathies, representing 62% of patients with idiopathic necrotizing myopathies.³⁹ Of those 16 antibody-positive cases, 10 were previously exposed to statins. These novel autoantibodies are not commercially available at this time.

Electrophysiology

Needle electromyography (EMG) shows increased insertional and spontaneous activity, with small-amplitude low-frequency fibrillation potentials and positive sharp waves, and occasionally pseudomyotonic and complex repetitive discharges indicating chronicity. Electrical myotonia is a prominent finding in SANAM. Muscle fibrosis in advanced cases may result in reduced insertional activity. Motor unit action potentials (MUAPs) are polyphasic, brief, and of low amplitude. MUAP recruitment is early/increased. With chronicity, reinnervation of split fibers produces MUAPs of increased duration. EMG is helpful in assessing relapsing weakness during treatment with corticosteroids. Worsening strength in the absence of fibrillation potentials suggests a steroid-induced myopathy.

Muscle Imaging

New diagnostic criteria may allow the use of muscle magnetic resonance imaging (MRI) signal abnormality in support of probable PM.⁹ Fat-suppressed and short tau inversion recovery skeletal muscle MRI may show fibrosis or diffuse or patchy signal symmetric increase in the proximal muscles and intermuscular fascia indicative of muscle edema due to inflammation. There is a relative sparing of the adductor, obturator, and pectineus muscles.⁴⁰ Fat deposition on T1-weighted images usually appears after 3 to 5 months of disease duration and preferentially involves the hamstrings. A proficiently performed EMG and clinical evaluation are sufficient for the selection of the optimal muscle to biopsy in most patients.

Muscle Histopathology and Pathogenesis

Dermatomyositis

Muscle biopsy is critical for the diagnosis of DM. The earliest detectable histologic abnormality is deposition of the C5b-9 or membrane attack complex (MAC) of complement around small blood vessels.^{41,42} This humorally mediated micro-angiopathy leads to decreased capillary density, especially at the periphery of the fascicle. MAC deposition is highly sensitive and specific in differentiating DM from other idiopathic inflammatory myopathies. Capillary damage and myofiber atrophy are concentrated in regions distant

from the affected intermediate-sized perimysial vessels leading to watershed ischemia and myofiber atrophy and capillary damage near the avascular perimysium.⁴³

The majority of muscle biopsies demonstrate perifascicular atrophy, often without an inflammatory infiltrate. When present, the inflammatory infiltrate consists of predominantly perimysial and perivascular macrophages and B cells presenting a putative antigen to naïve CD4⁺ T-lymphocytes. This presentation is HLA class II restricted and leads to the maturation of CD4⁺ T cells, depending on the cytokine environment, into Th1, Th2, Th17, or Treg cells. Invasion of nonnecrotic fibers is not common. The end result of this humoral microangiopathy is myofibril necrosis in groups and regeneration.

On electron microscopy, the earliest recognized changes are tubuloreticular inclusions in the intramuscular arterioles and capillaries.⁴⁴ Myxovirus resistance protein (MxA) is interferon (IFN) inducible and colocalizes to the small intramuscular blood vessel inclusions and is thought to form tubuloreticular inclusions around RNA viruses.⁴⁵ Therefore, the endothelial cell tubuloreticular inclusions present in affected dermatomyositis muscle are thought to be biomarkers of type 1 IFN exposure (see below).

Recent evidence from DM muscle-derived microarrays studies had uncovered an increase in MHC I and immunoglobulin gene transcripts⁴⁶ and a robust increase in the expression of type 1 IFN-inducible genes up to 570-fold in addition to an abundant immunoglobulin gene transcript.⁴⁵ The expression of MxA is localized to 50% perifascicular muscle fibers in addition to diffuse perifascicular major histocompatibility complex I (MHC I) positivity. Type I IFNs are known to upregulate MHC expression, activate natural killer cell cytotoxicity, promote activated T-cell survival, and support DC maturation. Analysis of peripheral blood mononuclear cells demonstrates a high IFN- α/β signature that parallels disease activity in DM.⁴⁷ Interleukin 6 (IL-6), a proinflammatory cytokine, plays central roles in the regulation of both innate and adaptive inflammatory and immune responses, as well as both humoral and cell-mediated autoimmune reactions.⁴⁸ More recently, Liao et al measured IFN α , IFN β , and IFN ω protein in blood samples from patients with myositis (DM, PM, and IBM) and healthy volunteers and found that IFN β signature was uniquely associated with DM.⁴⁸

Emerging data suggest that not all CD4⁺ cells are T cells, and that 30 to 90% are CD4⁺ / CD3[−] also referred to as plasmacytoid dendritic cells (pDC).⁴⁵ The pDC are part of the innate immune system response to viral antigens and respond by producing a large amount of IFN1 once their Toll-like receptors (TLR-7 and TLR-9) bind to viral nucleic acids. TLR activation leads to the generation of cytokines and chemokines and to the maturation of antigen-presenting cells (APCs) by upregulating costimulatory molecules that promote efficient interactions between APCs and T cells. This IFN signature was also noted in the active phase of other autoimmune disorders. IFN signature is seen in DM skin, similar to that found in the blood and muscle of DM patients.⁴⁹

Polymyositis

Muscle biopsy is critical for the confirmation of PM and exclusion of mimics such as IBM, muscular dystrophy, acid maltase deficiency, and NM. The histologic features of PM are distinct from DM. Polymyositis is the result of an HLA-restricted cell-mediated cytotoxic immune response directed at muscle fibers. The prominent microscopic features are fiber size variability, scattered necrotic and regenerating fibers, and endomysial inflammation consisting primarily of activated CD8⁺ cytotoxic T cells, and macrophages, that in 63% of cases invade nonnecrotic muscle fibers³ expressing MHC-1 antigens. This histologic pattern is not distinctive as it occurs in all IBM patients. These pathologic findings indicate PM in most cases, while 37% have clinical evidence supportive of IBM.³ The MHC-1 antigens,

which are not constitutively expressed under normal conditions, may even be expressed on the surface of noninvaded intact myocytes. Surface expression of MHC-1 is not specific to the idiopathic inflammatory myopathies and can be seen in dystrophies and statin-induced myopathy. A sarcoplasmic reticular pattern of internal MHC-1 reactivity is characteristic.⁵⁰ It is thought that MHC-1 antigens express an unknown endogenous peptide that acts as the autoantigen. The endomysial CD8+ cytotoxic T cells are antigen-specific and destroy myocytes through the perforin pathway. These are accompanied by abundant myeloid dendritic cells that surround nonnecrotic fibers and act as APCs.⁵¹ Microarray experiments in PM indicate increased immunoglobulin gene expression.^{46,52} Immunoglobulins are secreted by endomysial plasma cells, and unlike DM, are not deposited in the muscle blood vessels.⁵² In a longitudinal study of 42 treated patients (21 DM and 21 PM), the type 1 IFN signature was significantly overexpressed in the blood of both DM and PM patients.⁵³ Only the type 1 IFN signature was significantly correlated with disease. There was no significant difference in the other cytokine signature scores (GM-CSF, IL-10, IL-13, IL-1 β , or TNF- α) between patients with low or moderate disease activity, and patients with high disease activity.

Necrotizing Myopathy

Muscle histopathology is central to the diagnosis of NM. The hallmark of all autoimmune NM is the presence of scattered necrotic myofibers with myophagocytosis in the absence or paucity of T-lymphocytic inflammation. Microvascular deposition of complement MAC suggests a humorally mediated microangiopathy. Unlike DM, perivascular inflammation is scant, and there are no endothelial tubuloreticular inclusions on EM. A variety of distinctive findings occur in specific subtypes of NM. Demonstration of thick-walled and enlarged “pipestem” capillaries of normal number is diagnostic of NM with pipestem capillaries.⁵⁴ Muscle connective tissue positively staining for alkaline phosphatase has been described in malignancy-associated NM. SRP-associated NM demonstrates a bimodal distribution of fiber sizes, increased endomysial connective tissue, and reduced endomysial capillary number with enlargement and thickening. Marked fibrosis is noted 5 months after onset. MAC is deposited on endomysial capillaries. Upregulation of MHC class I antigens was seen in a minority (9%) of idiopathic NM cases in one study.¹⁵ In another case series, 75% of NM cases demonstrated MHC class I expression and this involved 10% or more of the nonnecrotic fibers.⁵⁵

Muscle fibers of SANAM express on their surfaces MHC class I antigens in eight of eight biopsy specimens, supporting the notion of an immune-mediated NM induced by endoplasmic reticulum stress.⁵⁶ It is thought that the latter leads to exposure of neoantigens thereby activating the immune system despite statin cessation. Though the pathophysiology of SANAM is uncertain, it is likely humorally mediated via cytokine expression and complement activation.⁵⁶

The pathophysiology of NM has witnessed marked advances with the discovery of anti-200/100 autoantibodies.³⁹ These autoantibodies were identified by immunoprecipitation in 17 out of 213 patients with idiopathic inflammatory myopathy, 16 of whom had the pathology of NM and the remaining patient’s biopsy specimen was notable for extensive inflammatory infiltrates. Out of 38 NM cases, 12 had known causes, such as SRP antibodies and 16 of 26 remaining NM cases had the newly described 200/100 autoantibodies. Of these 16 NM cases, 10 were exposed to statins and six were not. Although close examination revealed endomysial and/or perivascular collections of inflammatory cells in five of the 16 muscle biopsy specimens, the degree of inflammation was mild compared with that seen in typical muscle biopsy specimens obtained from patients with PM or DM. Examination of frozen muscle tissue samples available in 8 of 16 patients revealed abnormally enlarged endomysial capillaries with thickened walls in five specimens with capillary density

preservation. Although endomysial capillaries did not stain for MAC, small perimysial vessels stained positive in six of eight muscle biopsy specimens. There was nonspecific MAC deposition on necrotic and degenerating myofibers. Unlike the findings of Needham et al,⁵⁷ only four of eight specimens demonstrated sarcolemmal MHC class I positivity.

Mamen et al subsequently identified the 100-kd antigen to be the 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR) protein.⁵⁸ In muscle biopsy tissue from antibody-positive patients, HMGCR expression was upregulated in cells expressing neural cell adhesion molecule, a marker of muscle regeneration. After statin cessation, high levels of HMGCR expression in regenerating muscle tissue might continue to drive the autoimmune response. Anti-HMGCR autoantibodies were found in 45 patients all of whom had the phenotype of NM and 30 (66.7%) had previously taken statins. Statins are known to dramatically upregulate HMGCR protein levels; thus, in some patients, increased HMGCR expression could trigger anti-HMGCR autoimmunity. All of the 40 available muscle biopsy samples were reported to show prominent NM pathology. Significant inflammatory infiltrates were noted in 20% of muscle biopsy samples. Patients who had not taken statins were clinically indistinguishable from those who had, except for their younger age. Although others have reported genetic variants and mutations in the *SLCO1B1*, *CYP*, and *COQ2* genes as determinants of statin myopathy susceptibility, the prevalence of the rs4149056 C allele was not increased in patients with anti-HMGCR. In the most recent publication, the majority of patients with and without statin exposure, including those with self-limited statin intolerance, did not develop anti-HMGCR antibodies.⁵⁹ Therefore, anti-HMGCR antibodies were felt to be highly specific for those with an autoimmune NM. Anti-HMGCR ELISA sensitivity and specificity were 94.4% and 99.3%, respectively, as compared with the gold standard of immunoprecipitation. In summary, the HMGCR autoantibody is present in 63% of NM cases with specificity approaching 100%. However, a puzzling finding is that 33% of antibody-positive NM cases are statin-naïve. Further studies from a larger diverse population of NM would be helpful to confirm these findings.

Therapy

Immunosuppressive therapy is the mainstay of treatment for DM, PM, and NM.⁶⁰ Autoimmune NM is often more resistant to immunosuppressive therapy than DM and PM, particularly if there is an underlying malignancy or a statin trigger. The overwhelming majority (23/25) of SANAM cases required more than one immunosuppressive agent with relapse in 12 cases following immunosuppressive therapy tapering.⁵⁶ As in DM and PM, many NM patients require the addition of other agents such as methotrexate (MTX) or azathioprine (AZA). For resistant or severe cases, intravenous immunoglobulin (IVIg) may be helpful. Third-line drugs include mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, etanercept, and cyclophosphamide.

There are very few published randomized controlled trials of immunosuppression in DM or PM. Those available compared placebo to azathioprine,⁶¹ plasma exchange,⁶² or IVIg.⁶³ Other, randomized controlled trials compared methotrexate with azathioprine,⁶⁴ cyclosporine with methotrexate,⁶⁵ and intravenous methotrexate with oral methotrexate plus azathioprine.^{61,64–66} The only positive controlled trials are a small crossover study of IVIg in DM⁶⁶ and a randomized double-blind, placebo-controlled trial of etanercept (50 mg subcutaneously weekly) for 52 weeks in 16 DM patients.⁶⁷

Corticosteroids

Although there are no controlled trials of corticosteroids, there is general agreement that they are effective in DM, PM, and NM. Corticosteroids can be used in a wide range of regimens and routes of administration. Prednisone 1 mg/kg/d (60–100 mg) is often given for

4 weeks followed by an abrupt or tapered conversion to an every other day schedule. A course of intravenous methylprednisolone may be administered first in patients with severe weakness. This taper is slower in patients with severe disease. A daily corticosteroid schedule is necessary in well-controlled hypertensive or nonbrittle diabetic patients. Although many patients feel immediately better after starting corticosteroids, strength improves over 2 to 3 months. An immediate response may suggest an alternate diagnosis such as polymyalgia rheumatica. Most patients remain on prednisone 60 to 100 mg every other day or its equivalent for the first several months. If no improvement is noted after 3 to 6 months, or if weakness reoccurs during the taper, a second-line immunosuppressive agent such as azathioprine, methotrexate, or IVIg is added. A second-line agent may be started earlier in patients with uncontrolled hypertension, diabetes, osteoporosis, obesity, and in those with baseline severe weakness. In those who respond, the dose is tapered by 20 mg per month until 40 mg every other day then by 10 mg per month until 20 mg every other day. After that, the dose is reduced by 5 mg every other day every 3 months to reach the minimal effective dose.

Methotrexate

Methotrexate (MTX), an antifolate that inhibits lymphocyte proliferation, is an effective and rapidly acting second-line steroid-sparing immunosuppressant. Methotrexate is started at a dose of 7.5 mg taken once weekly. The dose is increased 2 weeks later to 15 mg/week in two divided doses. The dose is then increased by 2.5 mg per week at 3 months, depending on the clinical response. The maximum weekly dose is 25 mg. Folic acid 0.8 to 1 mg per day orally is given to prevent stomatitis. Some advocate holding folic acid on the day of MTX administration.

Besides stomatitis, potential adverse events include bone marrow suppression, liver toxicity, alopecia, pneumonitis, teratogenicity, induction of malignancy, susceptibility to infections, and renal insufficiency. Complete blood count with differential and liver function tests are followed weekly for 1 month, then monthly for 6 months, then every 3 months thereafter while on a stable dose. Methotrexate-induced pneumonitis can be difficult to distinguish from myositis-associated interstitial lung disease. Thus, many experts do not use MTX in patients with known ILD or in those with Jo-1 antibodies.

Therapeutic effects of oral MTX are often noticeable after 4 to 8 weeks. If there is no improvement by that time, the dose may be increased. In nonresponders and in more severe cases, MTX may be given intravenously or intramuscularly at a dose of 0.4 to 0.8 mg per kg per week. The dose may be increased by 5 mg every week to a maximum of 60 mg weekly. Leucovorin rescue on the day after parenteral MTX administration is needed for doses as high as 50 mg.

Azathioprine

Azathioprine (AZA), an antimetabolite that blocks T-lymphocyte proliferation, is a very effective second-line steroid-sparing immunosuppressant with delayed onset of response. Azathioprine is administered in divided doses of 2 to 3 mg/kg/d, ranging from 100 to 250 mg per day. The clinical response begins in 4 to 8 months and peaks at 1 to 2 years. It is therefore not surprising that the 3-month placebo controlled trial of AZA did not show any efficacy.⁶⁰ However, hand-grip-strength improvement after 1 year was no different when comparing azathioprine to methotrexate.⁶⁴ Thiopurine methyltransferase deficiency predicts an increased risk of hematologic toxicity and enzyme activity may be measured prior to starting therapy. Azathioprine is contraindicated in homozygous patients whereas heterozygous patients should start at a lower dose.⁶⁸ A meta-analysis of 54 observational

studies and one randomized controlled trial did not demonstrate sufficient evidence to address the effectiveness of thiopurine methyltransferase activity pretesting.

A flulike reversible acute hypersensitivity reaction affects 12% of users in the first 2 weeks of therapy. It is associated with a rash, elevation in liver enzymes, and pancreatitis. Some may tolerate a rechallenge. Delayed adverse events include myelosuppression, hepatotoxicity, susceptibility to infection, malignancy, teratogenicity, rash, alopecia, fever, and arthralgias. Complete blood cell counts are measured weekly after initiating AZA then monthly.⁶⁹

Intravenous Immunoglobulin

IVIg has a complex immunomodulatory mechanism of action thought to involve reduced autoantibody production and binding, suppression of proinflammatory cytokines, Fc receptor blockade, increased macrophage colony stimulating factor and monocyte chemotactant protein-1, altered T cell function, decreased circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle. A randomized-controlled trial with optional crossover showed that IVIg 2 g/kg administered monthly for 3 months was very effective in 9 of 12 treatment-resistant DM patients.⁶³ Although prospective controlled trials are lacking, IVIg is also felt to be effective in PM^{70,71} and NM. American Academy of Neurology guidelines recommend IVIg as possibly effective for treating nonresponsive DM.⁷² IVIg is often used for patients with refractory disease or as a steroid-sparing agent. An initial dose of 2 g/kg is divided over 2 to 5 days. Maintenance dosing is 0.4 to 2 g/kg per month administered every 1 to 4 weeks.

Treatment of Refractory Patients

Treatment options for patients refractory to first- and second-line therapy include mycophenolate mofetil,⁷³ rituximab,^{74,75} or cyclophosphamide. Other third-line drugs include etanercept,⁶⁷ cyclosporine, tacrolimus,⁷⁶ and chlorambucil.⁷⁷ A large, multicenter clinical trial randomized 200 DM, JDM, and PM patients with refractory disease to receive rituximab early (Group A) or 8 weeks later (Group B). The primary endpoint measure was the time to achieve the definition of improvement (DOI) on two consecutive visits between both groups. The study lasted 44 weeks. There were no significant differences between Group A and B in the primary (20.2 and 20.0 weeks respectively) or secondary endpoints. The proportion of early and late rituximab patients achieving DOI at week 8 was 21% and 15%, respectively ($p = 0.32$).⁷⁸ It is likely that the study delayed treatment design hampered the detection of a significant benefit of rituximab as 83% of refractory cases met the DOI following rituximab treatment. In a small uncontrolled study, rituximab improved six of eight refractory SRP-positive patients on manual muscle strength and/or resulted in CK decline as early as 2 months after treatment.⁷⁹

In a controlled trial of etanercept, five of 11 treated patients were successfully weaned off prednisone compared with none of the five placebo-treated patients.⁶⁷ The median of the average prednisone dosage after week 24 was lower in the etanercept group (1.2 mg/d) than in the placebo group (29.2 mg/d). Five etanercept-treated and one placebo-treated patient developed worsening DM rash. Although a case of refractory DM-ILD was successfully treated with adalimumab⁸⁰; another case of rheumatoid arthritis developed DM 4.5 years after treatment with this anti-TNF- α drug.⁸¹ It is likely in the latter case that DM was a manifestation of overlap syndrome rather than it being induced by adalimumab.

Idiopathic Inflammatory Myopathies Associated with Interstitial Lung Disease

Corticosteroids are the first-line drug for idiopathic inflammatory myopathies associated with ILD, but most patients require adjuvant immunomodulating drugs.⁸² In cases of ILD

refractory to steroids, mycophenolate mofetil,⁸³ cyclosporine, and tacrolimus have been shown to be effective second-line agents.⁷⁶ Early intervention with prednisolone and CSA combination therapy and tight control of the daily CSA dose by monitoring the blood level 2 hours postdosing improved pulmonary function testing (PFT) and chest imaging findings in DM cases with acute to subacute ILD.⁸⁴ Rituximab and cyclophosphamide are third-line options to arrest progression in cases of refractory ILD. A third of treated cases experienced resolution of pulmonary involvement, whereas 16% deteriorated.¹⁹ Factors predictive of poor ILD prognosis include older age, symptomatic ILD, lower values of vital capacity, and diffusing capacity for carbon monoxide, a pattern of interstitial pneumonia on high-resolution CT scan and lung biopsy, and steroid-refractory ILD. There is increased mortality rate in patients with deteriorating ILD as compared with those without ILD deterioration (47.1% vs 3.3%).

Physical Therapy

Physical and occupational therapy, orthotic devices, and exercise are important components of idiopathic inflammatory myopathies therapy, as early as 2 to 3 weeks from the acute phase.⁸⁵ Although other studies have reported the safety and benefits of resistive exercise in active patients 1 to 3 months into their treatment,⁸⁶ most of the studies have been in chronic PM or DM.⁸⁷ In severe cases, passive range of motion exercises are prescribed for 1 to 3 months or until strength and CK start to improve, at which point strengthening exercises are initiated. In patients with mild to moderate weakness, a strengthening program is started 2 to 4 weeks after steroid initiation. Because pain from arthralgia and possibly arthritis is relieved by joint flexion, early mobilization is important to prevent flexion contractures of large and small joints, especially in JDM. Creatine monohydrate supplementation may improve functional performance without significant adverse effects.⁸⁸

Prognosis

The prognosis of the idiopathic inflammatory myopathies is generally favorable with some exceptions. An associated malignancy portends a poor prognosis for recovery and increases mortality. SANAM is often resistant to treatment. Concomitant ILD Jo-1 or SRP antibodies predict a poorer prognosis. Overall, drug-free remissions are rare except in JDM. Recent series underline that only 20 to 40% of treated patients will achieve PM/DM remission, whereas 60 to 80% will experience a polycyclic or chronic continuous course of the disease.^{89,90} Mortality among PM/DM patients remains two- to threefold higher than the general population, with cancer, lung, cardiac complications, and infections being the most common causes of deaths.^{91,92} Poor prognostic factors in PM/DM patients include older age,⁹³ male gender, non-Caucasian ethnicity, longer symptom duration, ILD,⁹⁴ cardiac involvement, dysphagia,⁹⁵ cancer,⁹² and serum myositis-specific antibodies (including coexistence of anti-Ro52 and anti-Jo1 antibodies, presence of antisignal recognition particle antibody, anti-155/140, and anti-CADM-140 antibodies). Anti-SRP antibody is associated with acute onset of refractory necrotizing myositis and antibody titers correlate with CK levels and disease activity.⁹⁶ Anti-155/140 antibody is associated with malignancy, whereas the presence of anti-CADM-140 antibody is associated with amyopathic DM and rapidly progressive ILD.

References

1. Dimachkie MM, Barohn RJ. Idiopathic inflammatory myopathies. *Front Neurol Neurosci*. 2009; 26:126–146. [PubMed: 19349710]
2. van der Meulen MFG, Bronner IM, Hoogendijk JE, et al. Polymyositis: an overdiagnosed entity. *Neurology*. 2003; 61(3):316–321. [PubMed: 12913190]

3. Chahin N, Engel AG. Correlation of muscle biopsy, clinical course, and outcome in PM and sporadic IBM. *Neurology*. 2008; 70(6):418–424. [PubMed: 17881720]
4. Kuo CF, See LC, Yu KH, et al. Incidence, cancer risk and mortality of dermatomyositis and polymyositis in Taiwan: a nationwide population study. *Br J Dermatol*. 2011; 165(6):1273–1279. [PubMed: 21895620]
5. Quinter SD, Chiu YE, Lyon VB, Holland KE, Ruggeri SY, Drolet BA. Inverse Gottron's papules: an unusual cutaneous manifestation of juvenile dermatomyositis. *Pediatr Dermatol*. 2012; 29(5): 641–644. [PubMed: 22211376]
6. Schmeling H, Stephens S, Goia C, et al. Nailfold capillary density is importantly associated over time with muscle and skin disease activity in juvenile dermatomyositis. *Rheumatology (Oxford)*. 2011; 50(5):885–893. [PubMed: 21156669]
7. Shirani Z, Kucenic MJ, Carroll CL, et al. Pruritus in adult dermatomyositis. *Clin Exp Dermatol*. 2004; 29(3):273–276. [PubMed: 15115510]
8. Hundley JL, Carroll CL, Lang W, et al. Cutaneous symptoms of dermatomyositis significantly impact patients' quality of life. *J Am Acad Dermatol*. 2006; 54(2):217–220. [PubMed: 16443050]
9. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands. *Neuromuscul Disord*. 2004; 14(5):337–345. [PubMed: 15099594]
10. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med*. 1975; 292(8):403–407. [PubMed: 1089199]
11. Amato AA, Griggs RC. Unicorns, dragons, polymyositis and other mythical beasts. *Neurol (Tokyo)*. 2003; 61:288–289.
12. Amato AA, Barohn RJ. Idiopathic inflammatory myopathies. *Neurol Clin*. 1997; 15(3):615–648. [PubMed: 9227956]
13. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003; 362(9388):971–982. [PubMed: 14511932]
14. Pal S, Sanyal D. Jaw muscle weakness: a differential indicator of neuromuscular weakness—preliminary observations. *Muscle Nerve*. 2011; 43(6):807–811. [PubMed: 21607965]
15. Ellis E, Ann Tan J, Lester S, et al. Necrotizing myopathy: clinicoserologic associations. *Muscle Nerve*. 2012; 45(2):189–194. [PubMed: 22246873]
16. Suzuki S, Ohta M, Shimizu Y, Hayashi YK, Nishino I. Anti-signal recognition particle myopathy in the first decade of life. *Pediatr Neurol*. 2011; 45(2):114–116. [PubMed: 21763952]
17. Grable-Espósito P, Katzberg HD, Greenberg SA, Srinivasan J, Katz J, Amato AA. Immune-mediated necrotizing myopathy associated with statins. *Muscle Nerve*. 2010; 41(2):185–190. [PubMed: 19813188]
18. Tymms KE, Webb J. Dermatopolymyositis and other connective tissue diseases: a review of 105 cases. *J Rheumatol*. 1985; 12(6):1140–1148. [PubMed: 4093921]
19. Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. *Arthritis Rheum*. 2011; 63(11):3439–3447. [PubMed: 21702020]
20. Hochberg MC, Feldman D, Stevens MB, Arnett FC, Reichlin M. Antibody to Jo-1 in polymyositis/dermatomyositis: association with interstitial pulmonary disease. *J Rheumatol*. 1984; 11(5):663–665. [PubMed: 6334746]
21. Targoff IN, Miller FW, Medsger TA Jr, Oddis CV. Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol*. 1997; 9(6):527–535. [PubMed: 9375282]
22. Maoz CR, Langevitz P, Livneh A, et al. High incidence of malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. *Semin Arthritis Rheum*. 1998; 27(5):319–324. [PubMed: 9572713]
23. Sigurgeirsson B, Lindelöf B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med*. 1992; 326(6):363–367. [PubMed: 1729618]
24. Laxanpal S, Bunch TW, Ilstrup DM, Melton LJ III. Polymyositis-dermatomyositis and malignant lesions: does an association exist? *Mayo Clin Proc*. 1986; 61(8):645–653. [PubMed: 3724244]

25. Scaling ST, Kaufman RH, Patten BM. Dermatomyositis and female malignancy. *Obstet Gynecol.* 1979; 54(4):474–477. [PubMed: 492630]
26. Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am.* 1997; 23(3):619–655. [PubMed: 9287380]
27. Chen YJ, Wu CY, Huang YL, Wang CB, Shen JL, Chang YT. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. *Arthritis Res Ther.* 2010; 12(2):R70. [PubMed: 20398365]
28. Miller T, Al-Lozi MT, Lopate G, Pestronk A. Myopathy with antibodies to the signal recognition particle: clinical and pathological features. *J Neurol Neurosurg Psychiatry.* 2002; 73(4):420–428. [PubMed: 12235311]
29. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *PLoS ONE.* 2012; 7(3):e33442. [PubMed: 22438933]
30. Eimer MJ, Brickman WJ, Seshadri R, et al. Clinical status and cardiovascular risk profile of adults with a history of juvenile dermatomyositis. *J Pediatr.* 2011; 159(5):795–801. [PubMed: 21784434]
31. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol.* 2011; 18(1):19–e3. [PubMed: 20880069]
32. Fathi M, Barbasso Helmers S, Lundberg IE. KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis. *J Intern Med.* 2012; 271(6):589–597. [PubMed: 21950266]
33. Gono T, Kawaguchi Y, Sugiura T, et al. Interleukin-18 is a key mediator in dermatomyositis: potential contribution to development of interstitial lung disease. *Rheumatology (Oxford).* 2010; 49(10):1878–1881. [PubMed: 20601655]
34. Ichimura Y, Matsushita T, Hamaguchi Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. *Ann Rheum Dis.* 2012; 71(5):710–713. [PubMed: 22258483]
35. Joffe MM, Love LA, Leff RL, et al. Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med.* 1993; 94(4):379–387. [PubMed: 8386437]
36. Suzuki S. Anti-SRP myopathy. *Rinsho Shinkeigaku.* 2011; 51(11):961–963. [PubMed: 22277439]
37. Kao AH, Lacomis D, Lucas M, Fertig N, Oddis CV. Anti-signal recognition particle autoantibody in patients with and patients without idiopathic inflammatory myopathy. *Arthritis Rheum.* 2004; 50(1):209–215. [PubMed: 14730618]
38. Hanisch F, Müller T, Stoltenburg G, Zierz S. Unusual manifestations in two cases of necrotizing myopathy associated with SRP-antibodies. *Clin Neurol Neurosurg.* 2012; 114(7):1104–1106. [PubMed: 22306424]
39. 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(9):2757–2766. [PubMed: 20496415]
40. Degardin A, Morillon D, Lacour A, Cotten A, Vermersch P, Stojkovic T. Morphologic imaging in muscular dystrophies and inflammatory myopathies. *Skeletal Radiol.* 2010; 39(12):1219–1227. [PubMed: 20449587]
41. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. *N Engl J Med.* 1986; 314(6):329–334. [PubMed: 3945256]
42. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. *Ann Neurol.* 1990; 27(4):343–356. [PubMed: 2353792]
43. Pestronk A, Schmidt RE, Choksi R. Vascular pathology in dermatomyositis and anatomic relations to myopathology. *Muscle Nerve.* 2010; 42(1):53–61. [PubMed: 20544925]
44. De Visser M, Emslie-Smith AM, Engel AG. Early ultrastructural alterations in adult dermatomyositis. Capillary abnormalities precede other structural changes in muscle. *J Neurol Sci.* 1989; 94(1–3):181–192. [PubMed: 2614466]
45. Greenberg SA, Bradshaw EM, Pinkus JL, et al. Plasma cells in muscle in inclusion body myositis and polymyositis. *Neurology.* 2005; 65(11):1782–1787. [PubMed: 16344523]

46. Zhou X, Dimachkie MM, Xiong M, Tan FK, Arnett FC. cDNA microarrays reveal distinct gene expression clusters in idiopathic inflammatory myopathies. *Med Sci Monit.* 2004; 10(7):BR191–BR197. [PubMed: 15232492]
47. Walsh RJ, Kong SW, Yao Y, et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. *Arthritis Rheum.* 2007; 56(11): 3784–3792. [PubMed: 17968926]
48. Liao AP, Salajegheh M, Nazareno R, Kagan JC, Jubin RG, Greenberg SA. Interferon β is associated with type I interferon-inducible gene expression in dermatomyositis. *Ann Rheum Dis.* 2011; 70(5):831–836. [PubMed: 21177291]
49. Wong D, Kea B, Pesich R, et al. Interferon and biologic signatures in dermatomyositis skin: specificity and heterogeneity across diseases. *PLoS ONE.* 2012; 7(1):e29161. [PubMed: 22235269]
50. Salaroli R, Baldin E, Papa V, et al. Validity of internal expression of the major histocompatibility complex class I in the diagnosis of inflammatory myopathies. *J Clin Pathol.* 2012; 65(1):14–19. [PubMed: 22075187]
51. Greenberg SA, Pinkus GS, Amato AA, Pinkus JL. Myeloid dendritic cells in inclusion-body myositis and polymyositis. *Muscle Nerve.* 2007; 35(1):17–23. [PubMed: 16969836]
52. Greenberg SA, Pinkus JL, Pinkus GS, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. *Ann Neurol.* 2005; 57(5):664–678. [PubMed: 15852401]
53. Greenberg SA, Higgs BW, Morehouse C, et al. Relationship between disease activity and type I interferon- and other cytokine-inducible gene expression in blood in dermatomyositis and polymyositis. *Genes Immun.* 2012; 13(3):207–213. [PubMed: 21881594]
54. Emslie-Smith AM, Engel AG. Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular infiltration. *Neurology.* 1991; 41(6):936–939. [PubMed: 2046947]
55. Needham M, Fabian V, Knezevic W, Panegyres P, Zilko P, Mastaglia FL. Progressive myopathy with up-regulation of MHC-I associated with statin therapy. *Neuromuscul Disord.* 2007; 17(2): 194–200. [PubMed: 17241784]
56. Niewold TB, Wu SC, Smith M, Morgan GA, Pachman LM. Familial aggregation of autoimmune disease in juvenile dermatomyositis. *Pediatrics.* 2011; 127(5):e1239–e1246. [PubMed: 21502224]
57. Bronner IM, Hoogendijk JE, Wintzen AR, et al. Necrotising myopathy, an unusual presentation of a steroid-responsive myopathy. *J Neurol.* 2003; 250(4):480–485. [PubMed: 12700915]
58. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum.* 2011; 63(3):713–721. [PubMed: 21360500]
59. Mammen AL, Pak K, Williams EK, et al. Rarity of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies in statin users, including those with self-limited musculoskeletal side effects. *Arthritis Care Res (Hoboken).* 2012; 64(2):269–272. [PubMed: 21972203]
60. Amato AA, Barohn RJ. Inclusion body myositis: old and new concepts. *J Neurol Neurosurg Psychiatry.* 2009; 80(11):1186–1193. [PubMed: 19864656]
61. Bunch TW, Worthington JW, Combs JJ, Ilstrup DM, Engel AG. Azathioprine with prednisone for polymyositis. A controlled, clinical trial. *Ann Intern Med.* 1980; 92(3):365–369. [PubMed: 6986827]
62. 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]
63. 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]
64. Miller J, Walsh Y, Saminaden S, Lecky BRF, Winer JB. Randomised double blind controlled trial of methotrexate and steroids compared with azathioprine and steroids in the treatment of idiopathic inflammatory myopathy. *J Neurol Sci.* 2002; 199(Suppl 1):S53.

65. Vencovský J, Jarosová K, Macháček S, et al. Cyclosporine A versus methotrexate in the treatment of polymyositis and dermatomyositis. *Scand J Rheumatol.* 2000; 29(2):95–102. [PubMed: 10777122]
66. Villalba L, Hicks JE, Adams EM, et al. Treatment of refractory myositis: a randomized crossover study of two new cytotoxic regimens. *Arthritis Rheum.* 1998; 41(3):392–399. [PubMed: 9506565]
67. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. *Ann Neurol.* 2011; 70(3):427–436. [PubMed: 21688301]
68. Evans WE, Hon YY, Bomgaars L, et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. *J Clin Oncol.* 2001; 19(8):2293–2301. [PubMed: 11304783]
69. Booth RA, Ansari MT, Loit E, et al. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. *Ann Intern Med.* 2011; 154(12):814–823. W-295–W-298. [PubMed: 21690596]
70. Cherin P, Piette JC, Wechsler B, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. *J Rheumatol.* 1994; 21(6):1092–1097. [PubMed: 7932419]
71. Danieli MG, Malcangi G, Palmieri C, et al. Cyclosporin A and intravenous immunoglobulin treatment in polymyositis/dermatomyositis. *Ann Rheum Dis.* 2002; 61(1):37–41. [PubMed: 11779756]
72. 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]
73. Rowin J, Amato AA, Deisher N, Cursio J, Meriggioli MN. Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology.* 2006; 66(8):1245–1247. [PubMed: 16636243]
74. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum.* 2005; 52(2):601–607. [PubMed: 15692974]
75. Noss EH, Hausner-Sypek DL, Weinblatt ME. Rituximab as therapy for refractory polymyositis and dermatomyositis. *J Rheumatol.* 2006; 33(5):1021–1026. [PubMed: 16541475]
76. Oddis CV, Scierba FC, Elmagd KA, Starzl TE. Tacrolimus in refractory polymyositis with interstitial lung disease. *Lancet.* 1999; 353(9166):1762–1763. [PubMed: 10347992]
77. Cagnoli M, Marchesoni A, Tosi S. Combined steroid, methotrexate and chlorambucil therapy for steroid-resistant dermatomyositis. *Clin Exp Rheumatol.* 1991; 9(6):658–659. [PubMed: 1764849]
78. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis (DM) and adult polymyositis (PM) – The RIM study. *Arthritis Rheum.* 2010; 62:3844.
79. Valiyl 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(9):1328–1334. [PubMed: 20506493]
80. Park JK, Yoo HG, Ahn DS, Jeon HS, Yoo WH. Successful treatment for conventional treatment-resistant dermatomyositis-associated interstitial lung disease with adalimumab. *Rheumatol Int.* 2011 Epub ahead of print.
81. Brunasso AM, Scocco GL, Massone C. Dermatomyositis during adalimumab therapy for rheumatoid arthritis. *J Rheumatol.* 2010; 37(7):1549–1550. [PubMed: 20595297]
82. Mimori T, Nakashima R, Hosono Y. Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. *Curr Rheumatol Rep.* 2012; 14(3):264–274. [PubMed: 22367479]
83. Morganroth PA, Kreider ME, Werth VP. Mycophenolate mofetil for interstitial lung disease in dermatomyositis. *Arthritis Care Res (Hoboken).* 2010; 62(10):1496–1501. [PubMed: 20506189]
84. Kotani T, Takeuchi T, Makino S, et al. Combination with corticosteroids and cyclosporin-A improves pulmonary function test results and chest HRCT findings in dermatomyositis patients with acute/subacute interstitial pneumonia. *Clin Rheumatol.* 2011; 30(8):1021–1028. [PubMed: 21340495]

85. Varjú C, Pethö E, Kutas R, Czirájk L. The effect of physical exercise following acute disease exacerbation in patients with dermato/polymyositis. *Clin Rehabil.* 2003; 17(1):83–87. [PubMed: 12617382]
86. Alexanderson H, Stenström CH, Jenner G, Lundberg I. The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. *Scand J Rheumatol.* 2000; 29(5):295–301. [PubMed: 11093595]
87. Alexanderson H. Exercise effects in patients with adult idiopathic inflammatory myopathies. *Curr Opin Rheumatol.* 2009; 21(2):158–163. [PubMed: 19339927]
88. Chung YL, Alexanderson H, Pipitone N, et al. Creatine supplements in patients with idiopathic inflammatory myopathies who are clinically weak after conventional pharmacologic treatment: Six-month, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2007; 57(4):694–702. [PubMed: 17471547]
89. Marie I, Hachulla E, Hatron PY, et al. Polymyositis and dermatomyositis: short term and longterm outcome, and predictive factors of prognosis. *J Rheumatol.* 2001; 28(10):2230–2237. [PubMed: 11669162]
90. Bronner IM, van der Meulen MF, de Visser M, et al. Long-term outcome in polymyositis and dermatomyositis. *Ann Rheum Dis.* 2006; 65(11):1456–1461. [PubMed: 16606652]
91. Limaye V, Hakendorf P, Woodman RJ, Blumbergs P, Roberts-Thomson P. Mortality and its predominant causes in a large cohort of patients with biopsy-determined inflammatory myositis. *Intern Med J.* 2012; 42(2):191–198. [PubMed: 21118413]
92. Airio A, Kautiainen H, Hakala M. Prognosis and mortality of polymyositis and dermatomyositis patients. *Clin Rheumatol.* 2006; 25(2):234–239. [PubMed: 16477398]
93. Marie I, Hatron PY, Levesque H, et al. Influence of age on characteristics of polymyositis and dermatomyositis in adults. *Medicine (Baltimore).* 1999; 78(3):139–147. [PubMed: 10352646]
94. Yamasaki Y, Yamada H, Ohkubo M, et al. Longterm survival and associated risk factors in patients with adult-onset idiopathic inflammatory myopathies and amyopathic dermatomyositis: experience in a single institute in Japan. *J Rheumatol.* 2011; 38(8):1636–1643. [PubMed: 21572147]
95. Dankó K, Ponyi A, Constantin T, Borgulya G, Szegedi G. Long-term survival of patients with idiopathic inflammatory myopathies according to clinical features: a longitudinal study of 162 cases. *Medicine (Baltimore).* 2004; 83(1):35–42. [PubMed: 14747766]
96. Benveniste O, Drouot L, Jouen F, et al. Correlation of anti-signal recognition particle autoantibody levels with creatine kinase activity in patients with necrotizing myopathy. *Arthritis Rheum.* 2011; 63(7):1961–1971. [PubMed: 21400483]

Table 1**Myositis-Specific Autoantibodies**

Name	Antigen	Manifestations
Jo-1	Histidyl tRNA synthetase	PM/DM and ILD
PL-7	Threonyl tRNA synthetase	PM/DM and ILD
PL-12	Alanyl tRNA synthetase	ILD > PM/DM
EJ	Glycyl tRNA synthetase	DM > PM and ILD
OJ	Isoleucyl tRNA synthetase	ILD and PM/DM
KS	Asparaginyl tRNA synthetase	ILD > PM/DM
Zo	Phenylalanyl tRNA synthetase	ILD and NM with inflammatory cells
SRP	Signal-recognition particle	Severe, acute, resistant NM
Mi-2	DNA helicase	Treatment-responsive DM
P155/140	Transcriptional intermediary factor 1-gamma (TIF- γ)	Cancer in adult DM; Severe cutaneous JDM
Anti-CADM 140	Melanoma differentiation associated gene 5 (MDA5)	Amyopathic DM; Rapidly progressive ILD
MJ	Nuclear matrix protein NXP-2	Most common in JDM; Rare in adult DM with cancer
Anti-SAE	Small ubiquitin-like modifier-activating enzyme	DM and ILD

DM, dermatomyositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; PM, polymyositis; NM, necrotizing myopathy.