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REVIEW

Idiopathic Inflammatory Myopathies: Current Trends in Pathogenesis, Clinical Features, and Up-to-Date Treatment Recommendations

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Abstract

Recently, there have been important advances in the understanding of the pathophysiologic features, assessment, and management of patients with a newly diagnosed idiopathic inflammatory myopathy (IIM). Myositis-specific autoantibodies have been identified to define patient subgroups and offer prognostic implications. Similarly, proinflammatory cytokines, such as interleukin 6 and type 1 interferon–dependent genes, may serve as potential biomarkers of disease activity in adult and juvenile patients with dermatomyositis (DM). Moreover, magnetic resonance imaging has become an important modality for the assessment of muscle inflammation in adult IIM and juvenile DM. Immune-mediated necrotizing myopathies also are being recognized as a subset of IIM triggered by medications such as statins. However, confusion exists regarding effective management strategies for patients with IIM because of the lack of large-scale, randomized, controlled studies. This review focuses primarily on our current management and treatment algorithms for IIM including the care of pediatric patients with juvenile DM. For this review, we conducted a search of PubMed and MEDLINE for articles published from January 1, 1970, to December 1, 2011, using the following search terms: *idiopathic inflammatory myopathies, dermatomyositis, polymyositis, juvenile dermatomyositis, sporadic inclusion body myositis, inclusion body myositis, inflammatory myositis, myositis, myopathies, pathogenesis, therapy,* and *treatment*. Studies published in English were selected for inclusion in our review as well as additional articles identified from bibliographies.

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The idiopathic inflammatory myopathies (IIMs) are a group of rare, systemic diseases that affect the muscles and result in proximal muscle weakness, muscle enzyme elevations, and extramuscular manifestations such as fever, weight loss, and rash. The IIMs are classified on the basis of patterns of presentation, age at onset, and immunohistopathologic features in skin and muscle biopsy specimens.[1-4] Dermatomyositis (DM) is characterized by an erythematous rash and symmetric proximal muscle weakness. Muscle biopsy reveals a mononuclear, inflammatory cell exudate arranged in a perivascular and perifascicular distribution with degenerating and regenerating muscle fibers and perifascicular atrophy.[3-11] Juvenile DM (JDM) affects children younger than 18 years and is characterized by proximal muscle weakness, calcinosis cutis, cutaneous vasculitis, ulcerations, and vasculopathy affecting the gastrointestinal tract.[12-15] Juvenile DM has similar histopathologic findings as adult DM, with perifascicular and perivascular inflammatory infiltrates, muscle degeneration and regeneration, and type I and type II fiber atrophy.[14] Polymyositis (PM) is characterized by symmetric proximal muscle weakness, and it has a distinct immunohistopathologic phenotype involving $CD8^+$ cytotoxic T cells invading nonnecrotic muscle fibers.[3-11] Immune-mediated necrotizing myopathy (IMNM) is a severe myopathy with minimal inflammatory infiltrate on muscle biopsy; it may be triggered by viral infections, medications such as statins, and malignant neoplasms.[16-21] Finally, sporadic inclusion body myositis (sIBM) has pathologic features that suggest a degenerative neuromuscular disease with muscle fiber vacuolization and an abnormal accumulation of amyloid-β and phosphorylated tau proteins thought to be analogous to Alzheimer disease.[22-26]

Emerging data suggest that the autoantibody status of patients with IIM defines phenotypes and predicts outcomes such as

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ARTICLE HIGHLIGHTS

- Myositis-specific autoantibodies may define subgroups of patients with idiopathic inflammatory myositis, suggest specific extramuscular organ involvement such as the pulmonary and cardiac systems, and may offer a long-term prognosis.
- Magnetic resonance imaging, T1-weighted, T2-weighted, and sequences using fat suppression techniques and short tau inversion recovery, provides useful information to identify a muscle site for biopsy, diagnose myositis, and monitor treatment response.
- For adult patients with idiopathic inflammatory myositis, we suggest an initial drug regimen of high-dose corticosteroids concurrent with a steroid-sparing agent, such as methotrexate, azathioprine, or mycophenolate mofetil, followed by a tapering course of corticosteroids.
- For juvenile dermatomyositis uncomplicated by severe disease, we begin corticosteroids at 2 mg/kg up to a maximum of 60 mg/d with a taper after 2 to 4 weeks, depending on patient response. Subcutaneous methotrexate is added at the onset of treatment at a dosage of 15 mg/m^2 once weekly.
- For adult or juvenile patients with severe myositis, extensive extramuscular organ involvement, or refractory disease, we use high-dose methylprednisolone in addition to intravenous immunoglobulin, cyclophosphamide, rituximab, or cyclosporine.
- Novel biomarkers of disease activity such as interleukin 6 and type I interferon–regulated genes may serve as indicators of disease activity in adult and juvenile myositis.

treatment response and extramuscular organ involvement. Myositis-specific autoantibodies (MSAs) may be found in the serum of approximately 50% to 60% of patients with IIM, and they are directed against proteins in the cell nucleus and cytoplasm. The common MSAs are the aminoacyl transfer RNA (tRNA), synthetases anti-p155/140 antibody (a 155-kDa reactive nuclear protein), anti-Mi2, anti-SRP, and anti-CADM-140, although there are many others used as markers to define subsets of IIM.[27-34] Moreover, novel biomarkers have been identified to potentially serve as serologic evidence of increased disease activity and to monitor treatment response. In particular, interleukin (IL) 6 and type 1 interferon genes and proteins may serve as markers for disease activity in DM.[35-39]

This review focuses on our current treatment recommendations. The approach to treatment of IIM has not been standardized because of the rarity of the disease and the lack of controlled treatment trials. Hence, universal agreement does not exist among myositis experts regarding treatment decisions and management strategies. Our institution has a standard protocol for the treatment of IIM that we will review. In addition, current literature regarding MSAs as predictors of clinical phenotypes and disease outcomes and novel biomarkers of disease activity will be discussed. We conducted a search of PubMed and MEDLINE for articles published from January 1, 1970, to December 1, 2011, using the following search terms: *idiopathic inflammatory myopathies, dermatomyositis, polymyositis, juvenile dermatomyositis, sporadic inclusion body myositis, inclusion body myositis, inflammatory myositis, myositis, myopathies, pathogenesis, therapy,* and *treatment.* Studies published in English were selected for inclusion in our review. Additional articles were obtained from retrieved article bibliographies.

CLINICAL AND LABORATORY FEATURES OF IIM

Dermatomyositis

Dermatomyositis presents with an erythematous, photosensitive rash with poikiloderma, Gottron papules, periorbital edema, heliotrope rash, and periungual telangiectasias. Rashes may involve the face, neck, torso, fingers, and extensor surfaces of the extremities. Infrequently, patients with DM have cutaneous vasculitis, ulcerations, and calcinosis, but these features are seen more often in JDM.[13-15] Symmetric proximal muscle weakness develops over weeks to months coupled with elevated muscle enzyme levels. Electromyographic (EMG) abnormalities include polyphasic motor unit action potentials of short duration and low amplitude and increased insertional and spontaneous activity with fibrillation potentials, sharp waves, and/or repetitive discharges. Other organ systems may be involved, such as vascular, pulmonary, gastrointestinal, and cardiac systems.[4,15] Pulmonary manifestations range from aspiration pneumonia due to weakness of the ventilatory muscles to interstitial lung disease (ILD). The most common ILD

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pattern is a nonspecific interstitial pneumonitis that has the appearance of ground-glass opacities without honeycombing on high-resolution computed tomography (CT) of the lungs; it can be seen in up to one-third of patients with DM or PM.[40] Interstitial lung disease may lead to complications such as pulmonary hypertension or cor pulmonale. Rarely, the ILD can be rapidly progressive and fatal.[40,41] Dysphagia related to proximal muscle dysfunction due to cricopharyngeal weakness or spasm may be evident on videofluoroscopy.[42] Cardiac manifestations may not be as symptomatic as other organ manifestations of DM. For example, an asymptomatic arrhythmia such as sinus tachycardia may be detected by electrocardiography, and diastolic dysfunction may be seen on echocardiography. Although severe cardiac manifestations are not typical in DM, myocarditis has been found on autopsy studies.[43,44]

A common set of criteria for the diagnosis of DM (also used for PM) is that proposed by Bohan and Peter[1,2]: (1) characteristic skin findings, (2) proximal muscle weakness, (3) elevated muscle enzyme levels, (4) a myopathic pattern on EMG, and (5) evidence of an endomysial, mononuclear inflammatory infiltrate on muscle biopsy. (Four of the 5 criteria must be present for a definite diagnosis of PM.[1,2])

Polymyositis

Polymyositis presents with symmetric, proximal muscle weakness without a rash, elevated muscle enzyme levels, and extramuscular organ involvement similar to that in DM, such ILD and myocarditis.[4,40,43] Polymyositis is a rarer entity. Some experts believe that patients may be misdiagnosed as having PM given its nonunique clinical features shared with other myopathies.[45]

Immune-Mediated Necrotizing Myopathy

Immune-mediated necrotizing myopathy is now being recognized as part of the group of IIMs and is best characterized as a necrotizing myopathy with minimal or no inflammatory infiltrate on muscle biopsy. Pathogenesis is hypothesized to be immune mediated with a trigger such as a drug, and it may be responsive to immunosuppressive treatment.[16-19] There are clinical distinctions between IMNM and a toxic or necrotizing myopathy: the course of a necrotizing myopathy may be self-limited, and recovery may occur after the offending agent is discontinued, occasionally over weeks to months.[17,18] Similarly, patients with IMNM may have high elevations of creatine kinase (CK) levels, greater than 10 times the upper limits of normal, with acute or subacute onset of proximal muscle weakness that may be severe. However, patients with IMNM may also have a chronic disease course. Management, in general, is similar to that for patients with DM or PM with respect to use of corticosteroids and other immunosuppressants as indicated for control of disease.[17-19] Triggers that have been identified include viruses, cancer, connective tissue diseases, and certain medications such as statins. Statin-induced necrotizing myopathy has been associated with an antibody against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) protein that is upregulated in regenerating muscle fibers.[19-21] Anti-HMGCR antibodies may become clinically useful for monitoring disease activity. Recently, Werner et al[21] found that anti-HMGCR correlated with CK levels and extremity strength; treatment was associated with decreased antibody levels and improved arm strength.

Sporadic Inclusion Body Myositis

Sporadic inclusion body myositis is distinctive among the IIMs because it is characterized by symmetric or asymmetric weakness of insidious onset involving the proximal and/or distal muscles occurring after age 50 years with a male to female ratio of 3:1.[22] Classically, atrophy of the forearm flexors, finger flexors, and quadriceps muscles is observed. Dysphagia may be a prominent feature leading to poor outcomes such as feeding tube placement or recurrent aspiration pneumonia. Muscle enzyme levels, such as the CK level, may be minimally elevated. A muscle biopsy reveals an inflammatory mononuclear cell infiltrate with rimmed vacuoles and congophilic deposits.[22-25] The Griggs criteria[26] that are frequently used for diagnosis address several clinical, laboratory, and histopathologic features: duration of illness longer than 6 months; age at onset older than 30 years; weakness of proximal and distal muscles of upper and lower extremities and either finger flexor weakness, wrist flexor greater than wrist extensor weakness, or quadriceps weakness; serum CK level less than 12 times normal; and muscle biopsy evidence of invasion of

nonnecrotic fibers by mononuclear cells, vacuolated muscle fibers, and intracellular amyloid deposits or 15- to 18-nm tubulofilaments on muscle biopsy. Patients have a definite diagnosis of sIBM if they satisfy the vacuolated muscle fibers criteria in addition to all the other criteria.[26]

Juvenile Dermatomyositis

Juvenile DM presents in patients less than 18 years of age with skin and muscle features similar to those in adult DM.[12,13] Traditionally, the Bohan and Peter criteria are employed for diagnosis.[1,2] However, on the basis of a 2006 international consensus survey of members of the Network for Juvenile Dermatomyositis and the Paediatric Rheumatology International Trials Organisation, criteria have been proposed to include features of muscle inflammation seen on magnetic resonance imaging (MRI) and/or ultrasonography, nailfold capillaroscopy, calcinosis cutis (soft tissue calcification), and dysphonia.[46,47] Nailfold capillaroscopy is particularly useful in predicting severity of disease and monitoring the clinical course in patients with JDM.[48] Extramuscular manifestations include Raynaud phenomenon, inflammatory arthritis, pneumonitis, vasculopathy of the gastrointestinal tract leading to bowel ischemia and/or infarction, and cardiomyopathy. Dysphagia is also a prominent clinical feature of JDM, with features of cricopharyngeal muscle dysfunction similar to adult DM.[13-15,49] Juvenile DM can be further classified on the basis of disease course, including monocyclic, polycyclic, chronic, and ulcerative disease. Monocyclic refers to a disease course characterized by remission within 2 to 3 years, while a polycyclic course is marked by periods of relapse.[13,50]

Although usually associated with systemic-onset juvenile idiopathic arthritis, macrophage activation syndrome may be present in children with JDM.[51,52] Macrophage activation syndrome is a severe, life-threatening, systemic inflammatory condition characterized by the presence of activated macrophages that phagocytose erythroid precursors in the marrow, leading to progressive cytopenias, fever, hepatosplenomegaly, and coagulopathy. Affected patients should be managed in a critical care setting, and treatment involves high-dose corticosteroids, cyclosporine, and anakinra, a recombinant IL-1 receptor antagonist.[52,53]

Amyopathic and Hypomyopathic Dermatomyositis

Two subsets of DM have been described, amyopathic DM and hypomyopathic DM. Criteria have been developed to classify these subsets. Patients with amyopathic DM have the classic rash seen in DM without evidence of muscle inflammation, as determined by normal muscle enzyme levels within 2 years after diagnosis and normal EMG findings.[54] Hypomyopathic DM refers to patients who do not have muscle weakness, but there may be evidence of muscle inflammation such as a mild elevation in CK level, abnormalities on EMG, inflammation detected by MRI of proximal muscles, and abnormalities in muscle biopsy specimens.[55] Interstitial lung disease has been described in patients with amyopathic DM.[56] Malignancy has also been reported in patients with amyopathic DM, although the incidence is lower than that found in classic DM.[55,57]

PATHOGENESIS

Our current understanding of the pathogenesis of IIM is that there is a combination of genetic and environmental factors that determine susceptibility to IIM.[58] Certain HLA alleles on chromosome 6, in particular HLA-DQA1*0501 and HLA-DRB1*0301, have been associated with IIM.[59,60] Polymorphisms in the tumor necrosis factor α (TNF-α) (TNFα-308A) allele have been associated with a longer disease course, increased disease severity, and calcinosis in JDM.[60,61] Viral infections, such as with Coxsackie B virus, may trigger the onset of immune dysregulation in the genetically susceptible host.[62] There are several important histologic differences among the inflammatory myopathies that suggest different pathogenic mechanisms.

Dermatomyositis and Juvenile Dermatomyositis

Dermatomyositis is a complement-mediated vasculopathy of the small vessels in muscle tissue resulting in ischemia and vessel damage. There is deposition of the C5b-9 membrane attack complex around the microvasculature.[10] Classic histopathologic findings are mononuclear cell infiltrates in muscle fibers, necrotic fibers, and degenerating and regenerating fibers. Perifasicular atrophy of the myofibrils may be seen, possibly related to tissue

hypoperfusion from ischemic microangiopathy in later stages of the muscle disease.[1-11] The mononuclear cell infiltrates consist of B cells and $CD4^+$ T cells in the perimysial and perivascular area and plasmacytoid dendritic cells (pDCs) in perifascicular areas, which supports a humorally mediated mechanism of pathogenesis.[3-10] Similarly, JDM has histopathologic features supporting a small-vessel vasculopathy or vasculitis as a pathogenic mechanism. Typical muscle biopsy findings of JDM include atrophy in the perifasicular areas from tissue hypoperfusion.[12-15] Common proinflammatory cytokines described in DM and JDM include type 1 interferons (α/β) and TNF-α. These cytokines may be present in muscle tissue and endothelial cells and may induce major histocompatibility complex (MHC) class I expression in normal and regenerating muscle cells.[3,4,9,63] Other cytokines that have been observed are IL-4, IL-6, IL-15, and IL-17. The proinflammatory cytokines predominate in muscle tissue, leading to migration of $CD4^+$ T cells such as Th1 and Th17, B cells, $CD8^+$ T cells, macrophages, and pDCs.[3-9,37,63-65] Dendritic cells are antigen-presenting cells that are now recognized as important mediators in the inflammatory response in DM and JDM. A type of dendritic cell, pDCs, have been found in the skin and muscle tissue of patients with DM and JDM.[64,66] They are known for producing type 1 interferon in response to viral nucleic acids.[67] Transforming growth factor β has been observed in muscle tissue, which may promote anti-inflammatory effects and fibrosis.[68] Chemokines are chemoattractants that promote development of inflammatory changes due to migration of leukocytes to muscle tissue; commonly described chemokines include the macrophage inflammatory proteins 1α (chemokine ligand 3) and 1β (chemokine ligand 4), which attract T and B cells, and B-cell chemokine CXCL13, which is prominent in perimysial infiltrates and is a B-cell activator.[69,70]

Polymyositis

In PM, an endomysial mononuclear cell infiltrate surrounds and invades nonnecrotic muscle fiber cells, causing muscle fiber necrosis and regeneration.[3-8] Unlike DM, the microvasculture of muscle tissue does not appear to be involved in its pathogenesis, and B cells are rarely seen. It is believed that a cellular-mediated cytotoxic mechanism accounts for its pathogenesis.[3,9] $CD8^+$ cytotoxic T cells and macrophages clonally expand and interact with muscle fibers expressing MHC class I, resulting in muscle fiber changes in the endomysium.[3-9] Polymyositis has the same proinflammatory cytokines and chemokines that are seen in DM, including type 1 interferons (α/β) and TNF-α.[4,9,63]

Sporadic Inclusion Body Myositis

As in PM, patients with sIBM have $CD8^+$ cytotoxic T cells and macrophages in the endomysium that surround and invade nonnecrotic muscle fiber cells, leading to muscle fiber necrosis in fibers expressing MHC class I.[3-8] Also similar to PM, a cellular-mediated cytotoxic mechanism is believed to be the primary feature of pathogenesis in sIBM.[3,9] Muscle degeneration in sIBM is characterized by rimmed vacuoles seen on light microscopy, nuclear and cytoplasmic inclusions detected on electron microscopy, congophilic amyloid deposits, and phosphorylated tau proteins.[4,22,24-26] Due to the degeneration seen on muscle histopathologic studies, sIBM has become increasingly considered a degenerative myopathy with inflammatory features.[23,24] As in DM and PM, proinflammatory cytokines circulate in sIBM, including type 1 interferons (α/β) and TNF-α.[4,9,63]

Immune-Mediated Necrotizing Myopathy

In IMNM, macrophages surround necrotic muscle fibers, and atrophic and regenerating fibers are present. Immunostaining reveals T lymphocytes (CD3) and macrophages (CD68) around necrotic and regenerating muscle fibers. The pathogenesis of IMNN is incompletely understood at this time, but macrophages may be the primary effector cell.[16-19] In addition, anti-SRP and the anti-HMGCR (200 and 100 kDa) proteins have been found in patients with IMNN, suggesting an antibody-mediated autoimmune mechanism of pathogenesis.[19-21]

MYOSITIS-SPECIFIC AUTOANTIBODIES

Immune dysregulation in IIM may result in antibodies against specific nuclear and cytoplasmic antigens (Table 1). Characteristic phenotypes may be associated with certain MSAs.[27] Common MSAs are the aminoacyl

TABLE 1. Myositis-Specific Autoantibodies, Clinical Associations, and Frequencies in Adult and Juvenile Idiopathic Inflammatory Myopathies

Autoantibody	Target autoantigen	Clinical features	Frequency (%)	
			IIM	JDM
Anti-synthetase	Aminoacyl-tRNA synthetase	Mechanic's hands, arthritis, Raynaud phenomenon, ILD, myositis, fever	30-40	1-5
Jo-1	Histidyl-tRNA synthetase		20	…
PL-7	Theronyl-tRNA synthetase		<5	…
PL-12	Alanyl-tRNA synthetase		<5	…
OJ	Isoleucyl-tRNA synthetase		<5	…
EJ	Glycyl-tRNA synthetase		<5	…
KS	Asparaginyl-tRNA synthetase		<5	…
Ha	Tyrosyl-tRNA synthetase		<1	…
Zo	Phenylalanyl-tRNA synthetase		<1	…
Anti-CADM-140	MDA5	Aggressive ILD in Asians	50-73 (Asians)	Unknown
Anti-p155/140	TIF1-γ	Malignancy	13-21	22-29
Anti-SRP	Signal recognition particle	Necrotizing myopathy	5-10	1-3
Anti-Mi2	Nuclear helicase	Classic DM skin features	<10	4-10
Anti-200/100	HMG-CoA reductase	Necrotizing myopathy	<10	Unknown

DM = dermatomyositis; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IIM = idiopathic inflammatory myopathy; ILD = interstitial lung disease; MDA5 = melanoma differentiation-associated gene 5; TIF1-γ = transcriptional intermediary factor 1 γ; tRNA = transfer RNA; ellipses = not applicable.
Adapted from *Arthritis Res Ther*,[34] with permission.

tRNA synthetases. These enzymes catalyze binding of amino acids to specific tRNAs. These autoantigens include the following: Jo-1, PL-7, PL-12, OJ, EJ, KS, Ha, and Zo.[27-30] The anti-Jo-1 antibody is the most common. It is found in approximately 20% of adult patients with IIM. Anti-Jo-1 is the hallmark antibody for the antisynthetase syndrome, which consists of fever, mechanic's hands, Raynaud phenomenon, myositis, ILD, and arthritis. The frequencies of the other anti-tRNA synthetases range from 1% to 5%.[27,28,34]

The anti-Mi2 antibody acts against a nuclear helicase involved in transcriptional activation. Patients have classic cutaneous features including Gottron papules, shawl sign, cuticle overgrowth, V-sign, and a heliotrope rash.[28-30] Ultraviolet light has been implicated, suggesting an environmental trigger in adult DM.[71]

The anti-SRP antibody is directed against the signal recognition particle. It is a 6-polypeptide complex that escorts newly synthesized proteins from the cytoplasm to the endoplasmic reticulum.[28-30] Patients with anti-SRP antibody have necrotizing myopathy, acute in onset, with dilated cardiomyopathy and a poor response to standard immunosuppression.[72,73]

Other MSAs are the p155/140 doublet kDa proteins and antimelanoma differentiation-association gene 5 (anti-MDA5) autoantibodies.[28-30,74,75] Autoantibodies to p155/140 doublet protein are associated with cancer with an 89% specificity and 70% sensitivity.[74,75] The anti-MDA5 antibody acts against the retinoic acid—inducible gene receptors involved in recognizing viral proteins. It has been described in Asians with amyopathic DM, although it can occur in non-Asian patients as well. The anti-MDA5 antibody has been associated with rapid onset of ILD and death.[30-32] The MSAs may be markers of disease, but recent studies suggest that certain MSAs, such as anti-Jo-1, trigger or help propagate immune dysregulation by becoming endogenous type 1 interferon inducers by peripheral blood mononuclear cells in vitro.[28,76]

In children, the frequency of MSAs is less than adults with myositis. Rarely, antisynthetases are detected. Rider et al[77] found MSAs in only 2 of 52 children tested; only one had anti-Jo-1 antibody, and the other had anti-PL-12 antibody. Similarly, Wedderburn et al[78] studied 99 children with JDM and overlap connective tissue disease; only 2

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of 24 children with JDM and scleroderma overlap had anti-Jo-1 antibodies. Clinical features in children with anti-Jo-1 antibodies are similar to those in adults with arthritis and ILD.[77,79] Other autoantibodies described in children are anti-MJ, anti-Mi2, and the p155/140 kDa protein. Curiously, although autoantibodies to the p155/140 kDa protein have been found in 29% of patients with JDM, their presence is not associated with cancer.[28,33] Rather, autoantibodies to the p140 kDa protein have been associated with calcinosis in JDM, with an odds ratio of 7.0.[33] The anti-SRP antibody is rarely seen in children, although it has been described in African American girls with juvenile PM.[80]

INITIAL DISEASE INVESTIGATIONS

The differential diagnosis of noninflammatory myopathies includes muscular dystrophy of late onset, limb-girdle dystrophy (ie, dysferlinopathies) with onset during adult years, adult-onset nemaline myopathy associated with monoclonal gammopathy, or myotonic dystrophy type 2.[81] It is important to remember that muscular dystrophy and mitochondrial myopathies should be included in the differential diagnosis in a patient presenting with proximal muscle weakness and elevated muscle enzyme levels. A muscle biopsy can help to distinguish among these neuromuscular diseases and genetic testing. Typical histopathologic features of muscular dystrophy include a reduction or absence of dystrophin with degenerating and regenerating muscle fibers and replacement of muscle with fat or connective tissue; there may be invasion of muscle fibers by mononuclear cells, leading to diagnostic confusion with PM.[82] Genetic testing for muscular dystrophy should include testing for the dystrophin gene.[83] Mitochondrial myopathies have the classic histopathologic abnormalities of subsarcolemmal and interfibrillar accumulation of mitochondria visualized on Gomori trichrome stain and "ragged red fibers" of glycogen and neutral lipids against a blue background of muscle fibers with reduction or absence of cytochrome c oxydase.[84] The differential list for noninflammatory myopathies also includes drug-induced myopathy, endocrine myopathy such as thyroid disorder or hyperparathyroidism, and metabolic and infectious myopathies. In children, the differential diagnosis should include Duchenne or Becker muscular dystrophy and an infectious myopathy related to acute viral illness such as coxsackievirus or influenza virus.[85]

Relevant laboratory studies are a complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone, sodium, potassium, bicarbonate, serum urea nitrogen, creatinine, magnesium, fasting calcium, phosphorus, magnesium, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, CK, and aldolase levels. In addition, a fasting glucose and lipid panel should be obtained to determine risk for diabetes or hyperlipidemia. It is important to measure the connective tissue disease autoantibodies as well because an antinuclear antibody and antibodies to the extractable nuclear antigens such as anti-SS-A, anti-SS-B, anti-Smith, anti-RNP, anti-Scl 70, and anti-centromere antibodies suggest that the myopathy may be secondary to a connective tissue disease, although a positive autoantibody result does not necessarily establish a connective tissue disease diagnosis. Occasionally, a panel for MSAs may define the clinical phenotype, which may help to confirm the diagnosis, especially in patients with atypical clinical presentations. Myositis-specific autoantibodies may also offer a prognosis for subsets of patients, such as those with tRNA synthetase antibodies. Myositis-specific autoantibody tests are typically sent to a large reference laboratory, and results may not be available for several weeks.

Additional tests should include an EMG and a muscle biopsy. Electromyography should be performed for 2 major reasons: (1) to confirm a myopathic process characterized by polyphasic motor unit action potentials of short duration and low amplitude with increased insertional and spontaneous activity with fibrillation potentials, sharp waves, or repetitive discharges and (2) to target a muscle for biopsy. A muscle biopsy is one of the most important investigative tools for differentiating an inflammatory from a noninflammatory myopathy and for subclassification purposes. It is also the gold criterion for confirming a diagnosis of IIM. To maximize the diagnostic yield and reduce sampling error, a weak muscle should be chosen for biopsy. Often this weakness is

demonstrated by EMG abnormalities of the affected muscle; the same muscle on the opposite side should be chosen for biopsy. If a muscle biopsy cannot be done or the results are inconclusive, a skin biopsy may help to confirm the diagnosis of DM, coupled with other supporting evidence. The typical histopathologic findings on skin biopsy examination are a vacuolar interface dermatitis with vacuolar changes of the epidermal basal layer, apoptosis, necrotic keratinocytes, and perivascular lymphocytic infiltrate and mucin deposition in the dermis.[86,87] This vacuolar interface pattern may be seen in lupus erythematosus as well; however, direct immunofluorescence should yield negative results in patients with DM and positive results in lupus.[87]

In IIM, although the muscle is the primary target, other organ systems may be affected. We recommend performing chest radiography and baseline pulmonary function testing including determination of maximal inspiratory and expiratory pressures. Reduced inspiratory pressures or poor effort from respiratory muscle weakness could potentially lead to poor outcomes such as aspiration pneumonia. A reduced diffusing capacity for carbon monoxide may suggest an ILD process. Chest radiographs may be insensitive to detecting subtle pulmonary changes from ILD; hence, high-resolution CT of the lungs should be performed. We also recommend echocardiography if the suspicion for cardiac involvement is high.

Malignancy in Adults With IIM

Malignancy occurs in 25% of adult patients with DM within 0 to 5 years of disease onset. In PM, the association is approximately 10% to 15%.[88-91] Malignancy has also been associated with amyopathic dermatomyositis.[55,57] Breast and ovarian cancers are common in women, whereas lung and prostate cancers predominate in men. Other cancers associated with myositis include pancreatic, gastric, colorectal, and bladder cancer and non-Hodgkin lymphoma.[88-91] Practices differ among clinicians when evaluating for malignancy. Our practice is to perform age-appropriate cancer screening tests, including mammography, colonoscopy, prostate-specific antigen measurement, and prostate and pelvic examinations. An elevated CA-125 level at DM diagnosis in women may be predictive of increased risk for ovarian or primary peritoneal malignancy.[92] Computed tomography of the abdomen/pelvis or pelvic ultrasonography facilitates identification of a malignancy of ovarian, endometrial, or primary peritoneal origin. If resources allow, positron emission tomography may be useful if findings on initial studies are unremarkable but the suspicion for cancer remains high; however, there are no guidelines, to our knowledge, that recommend performing positron emission tomography as part of the malignancy evaluation.

Malignancy in Children With IIM

Malignancy is rare in children with JDM. In 1993, Sherry et al[93] described 6 children who had a paraneoplastic phenomenon involving PM and cancer. A recent literature review from 1963 to 2008 identified 12 children with JDM or PM and malignancy occurring within a range of 0 to 44 months from myositis diagnosis; these children were commonly diagnosed as having lymphoma or leukemia and had unexpected examination findings such as hepatosplenomegaly and extensive lymphadenopathy.[94] In general, in the absence of suggestive examination findings, an exhaustive evaluation for an underlying malignancy is not warranted in children with newly diagnosed myositis.

Imaging

Magnetic resonance imaging has become a diagnostic modality routinely used to confirm myositis. Indeed, evolving guidelines for diagnosing JDM have resulted in increased use of muscle MRIs.[46,47] We obtain MRIs of the proximal muscle groups in children with JDM to avoid invasive testing such as an EMG or muscle biopsy. Magnetic resonance imaging, T1-weighted, T2-weighted, and sequences using fat suppression techniques and short tau inversion recovery, provides useful information to diagnose myositis, monitor treatment response, and identify a muscle site for biopsy.[95-100] T1-weighted images may show muscle atrophy and chronic muscle damage.[96] T2-weighted images are used in active JDM because increased signal in muscle tissues suggests muscle edema, and T2-weighted relaxation times are a quantitative measure of muscle inflammation and correlate with disease activity.[97,98,100] Magnetic resonance imaging also may document fat

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atrophy on T2-weighted images. In DM, the connective tissue septa and muscle fascia may be involved.[96,99] Recently, a novel MRI-based scoring system using a 4-point scale indicating degree of muscle inflammation has been developed for objective assessment of active JDM using short tau inversion recovery—weighted axial images of the thighs, with a focus on 4 muscle groups—gluteal, hamstrings, quadriceps, and adductors.[101]

Magnetic resonance elastography is an experimental imaging method used to quantify mechanical elasticity of muscle and tissue. The method involves shear waves that are generated and propagated on MRI with postprocessing performed to produce a quantitative map of tissue elasticity.[102,103] McCollough et al[103] evaluated 9 patients with active myositis (DM, PM, JDM) and found reduced stiffness of the vastus medialis in the relaxed state in these patients compared to healthy controls. The usefulness of magnetic resonance elastography has not been established in clinical practice to date.

TREATMENT GUIDELINES

The major goals of treatment are to eliminate inflammation, restore muscle performance, and prevent chronic muscle disease and other organ system damage to reduce morbidity and regain quality of life. Therapy for newly diagnosed IIM involves a multidisciplinary approach with specialists depending on disease manifestations, including rheumatologists, neurologists, dermatologists, pulmonologists, physical therapists, speech therapists, occupational therapists, and orthopedic surgeons.

Initial Treatment Approach to Adult Patients With IIM

At diagnosis of IIM in adults, we initiate treatment with high-dose corticosteroids and a steroid-sparing agent (Figure 1). The rationale for corticosteroid use stems from early studies documenting improvement in muscle inflammation.[104,105] Lundberg et al[105] found decreased expression of class I MHC antigens including IL-1α, IL-1β, and cell adhesion molecules and improved muscle strength in adult patients treated with prednisolone for 3 to 6 months. We initiate prednisone at a dosage of 0.5 to 1 mg/kg per day, which typically is 60 to 80 mg/d as a single daily dose, with a taper after 2 to 4 weeks depending on patient response. We taper the dosage by 10 mg every 2 weeks to a dosage of 30 mg/d. At that time, the taper is slowed by 5 mg every 2 weeks until the dosage reaches 20 mg/d. Once the 20-mg/d dosage is achieved, the taper is slowed by 2.5 mg every 2 weeks until the taper is completed. Occasionally, at 10 mg/d the taper may be slowed by 1 mg every 2 to 4 weeks until completed.

Concurrent with corticosteroids, we administer an immunosuppressive drug to function as a steroid-sparing agent. Typically, these medications are slow acting and may take up to 3 to 6 months to reach full efficacy. The usual choices are methotrexate (MTX), azathioprine, and mycophenolate mofetil (MMF) (Figure 1). No trials have shown the superiority of one of these agents over the others. Bunch et al[106] showed that patients treated with azathioprine at a dosage of 2 mg/kg for 3 months in a controlled, double-blind trial improved muscle strength, but there was no significant difference compared with controls. A long-term follow-up trial demonstrated improvement in functional disability at 3 years in patients treated with prednisone and azathioprine.[107] If azathioprine is chosen, we check the patient's thiopurine methyltransferase level to screen for enzyme deficiency. Myelosuppression can occur in patients with a thiopurine methyltransferase deficiency who are treated with standard dosages of azathioprine. The goal dosage should be 2 mg/kg of ideal body weight in divided doses. Typically, we begin at 25 to 50 mg/wk with increments of 25 to 50 mg/wk until the goal dosage is reached. Common adverse effects include nausea and loose stools; less common adverse effects include fever and liver toxicity.

Methotrexate has been used since the 1970s to treat IIM. Metzger et al[108] demonstrated improvement in 17 of 22 patients with DM or PM treated with intravenous MTX, with normalization of the CK level and improvement in strength. If MTX is chosen, we begin with an initial dosage of 15 mg orally once weekly with 1 mg/d of folic acid supplementation because MTX is an antagonist of folate metabolism. We initiate MTX at a lower dosage in an effort to avoid potential intolerance or adverse effects. We aim for an MTX target dosage of 25 mg once weekly within 3 to 6 months. As with azathioprine use, transaminitis and

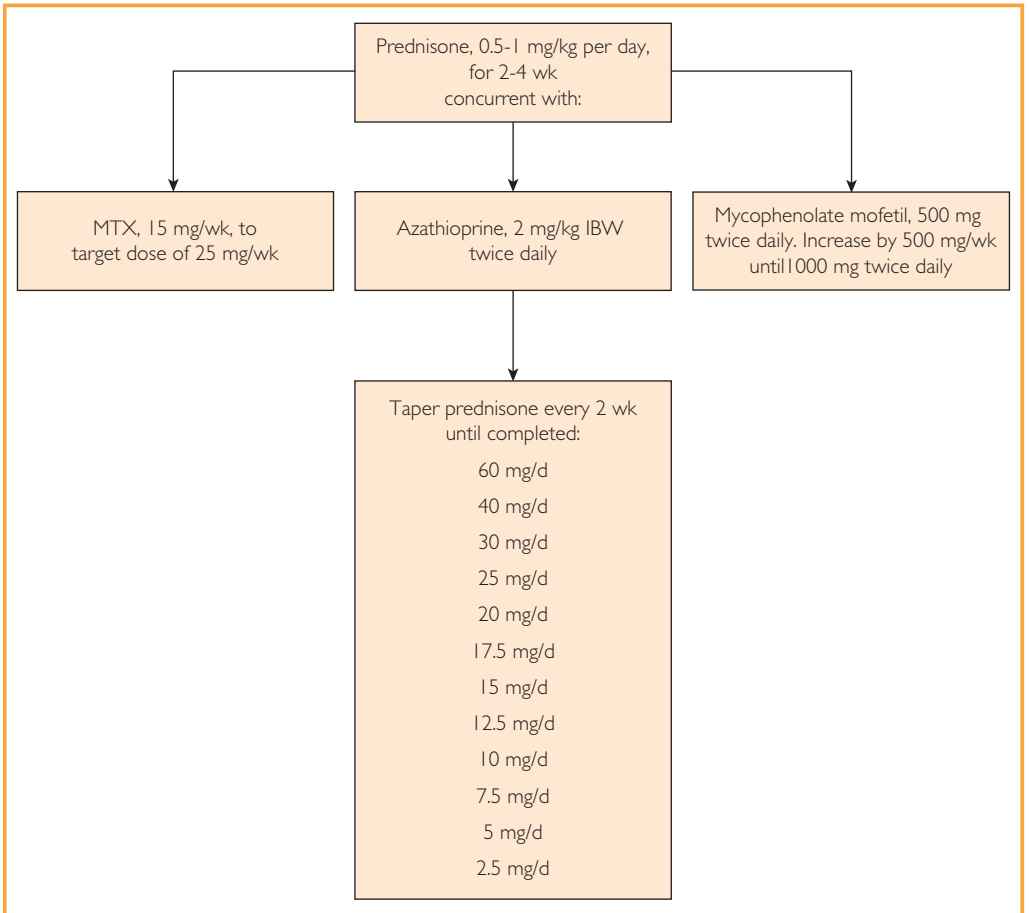

FIGURE 1. Initial management of uncomplicated, newly diagnosed idiopathic inflammatory myopathy in adult patients. IBW = ideal body weight; MTX = methotrexate.

gastrointestinal adverse effects are common in patients taking MTX. To avoid the potential for MTX-induced liver toxicity, we counsel patients to avoid excessive alcohol use. Screening for preexisting liver disease with baseline liver function tests and measurement of antibodies for hepatitis B and hepatitis C should be done before initiating MTX. Screening for lung disease is also advised; MTX-induced pneumonitis is a rare adverse effect that may be indistinguishable from ILD associated with a connective tissue disease. However, the presence of ILD is not an absolute contraindication for MTX use. Painful stomatitis can be a complication among adult patients with myositis. Higher doses of folic acid and leucovorin may be used as rescue therapy for MTX toxicities. Women of childbearing potential should be counseled to use a reliable form of birth control while taking MTX because it is teratogenic.

Certain follow-up studies are done to ensure toleration of treatment. Within 2 to 4 weeks of starting MTX or azathioprine, a complete blood cell count, liver enzyme function tests, and creatinine measurement should be obtained once a month for 3 consecutive months. Once a stable dosage is achieved, laboratory follow-up every 2 to 3 months thereafter is appropriate.[109]

Mycophenolate mofetil has emerged as an efficacious drug to treat IIM. It is an inhibitor of inosine monophosphate dehydrogenase, which affects de novo purine synthesis and T- and B-cell proliferation. Several retrospective case series have shown its efficacy in the treatment of severe DM and PM. Gelber et al[110] reported a case series of 4 patients who had DM with severe skin disease who benefitted from MMF therapy. Edge et al[111] found that 10 of 12 patients who had myositis with severe skin

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disease had improvement after 4 to 8 weeks of MMF. Patients with IIM who have pulmonary complications (eg, anti-synthetase syndrome) may respond favorably to MMF. In a small series, Morganroth et al[112] retrospectively studied 4 of 16 patients who had DM with ILD and found that 3 of the 4 had complete normalization of pulmonary function at 1-year follow-up. However, although ILD may affect up to 20% of adult patients with IIM, large-scale, controlled treatment trials are lacking to date. In adult patients with IIM, we initiate MMF at a dosage of 500 mg twice daily and increase the dosage by 500 mg every week, sometimes every 2 weeks depending on drug tolerability, up to a goal dosage of 2 g/d (1000 mg twice daily). Infrequently, the dosage may be increased to 3 g/d (1500 mg twice daily) if tolerated. Some physicians may monitor the MMF level (glucuronide) to ensure that the drug is within the therapeutic range. Compliance may become an issue in the higher dosage ranges because of adverse effects, commonly nausea and loose stools. Laboratory evaluation is essential to monitor for leukopenia or transaminitis. Women of childbearing potential should be counseled to use 2 reliable forms of birth control because MMF is also teratogenic.

For adult patients with IIM who have dysphagia, notable weight loss, severe rash, or weakness, we use intravenous immunoglobulin (IVIG) at a dosage of 1 to 2 g/kg of ideal body weight, usually given over 2 consecutive days (1 g/kg each on day 1 and day 2) once a month for 1 to 6 months. The serum IgA level should be checked before administering IVIG because IgA deficiency may lead to fever, infusion reactions, and/or severe anaphylaxis that is believed to be caused by macromolecular complexes formed between the infused IgA and anti-IgA antibodies.[113] If IgA deficiency is detected, the patient should receive an IVIG preparation with reduced IgA levels. If the dose of IVIG is higher than 80 g, we occasionally administer the dose over 3 to 5 days at 0.4 g/kg. The rationale for IVIG use comes from a placebo-controlled trial of 15 patients with DM who received IVIG every month for 3 months with option for crossover. Twelve patients had improvement in muscle strength, rash, and activities of daily living (ADL). Repeated muscle biopsies in 5 patients who received IVIG treatment showed an increase in muscle fiber diameter, resolution of complement deposits in capillaries, and a reduction in MHC class I antigens.[114] Several mechanisms of action may account for its effects: blocking of Fc receptors, inhibition of complement activation, influencing antigen recognition by sensitized T cells, and modulation of Fc-receptor mediated activity leading to down-regulation of phagocytosis.[113,115] However, the favorable effect of IVIG on muscle inflammation observed in muscle tissue biopsy specimens could not be repeated in a later study that included 13 treatment-resistant patients with DM, JDM, PM, and inclusion body myositis.[116]

Treatment Approach for Adult Patients With Severe IIM or Disease Refractory to Conventional Therapy

Patients with IIM that are refractory to standard therapy or who present with severe cutaneous disease, severe muscle weakness, and/or dysphagia with notable weight loss are treated with intravenous methylprednisolone (IVMP) at dosages of 500 mg to 1000 mg daily for 1-3 consecutive days followed by high-dose oral corticosteroids with taper (Figure 2). A case series reported by Bolosiu et al[117] involving 7 patients with IIM treated with IVMP daily for 3 days once monthly for 3 months demonstrated improvement in CK levels. Common adverse effects of high-dose corticosteroids include sleep disturbances, exacerbation of mood disorders such as anxiety or depression, psychosis, hypertension, and hyperglycemia.

We reserve the use of cyclophosphamide (CYC), either oral or intravenous, for severe organ manifestations. There are limited studies regarding the use of CYC in IIM with pulmonary complications. Yamasaki et al[118] conducted an open-label study of 17 patients with DM/PM or amyopathic DM treated with CYC and prednisolone. They found that 11 of the 17 patients had improvement in dyspnea, and 8 of the 17 patients had a 10% improvement in vital capacity and regression of lung fibrosis on high-resolution lung CT. Unfortunately, CYC is associated with cytopenias, hemorrhagic cystitis, premature ovarian failure, sterility, severe infections, nausea, and vomiting. The typical intravenous dosage

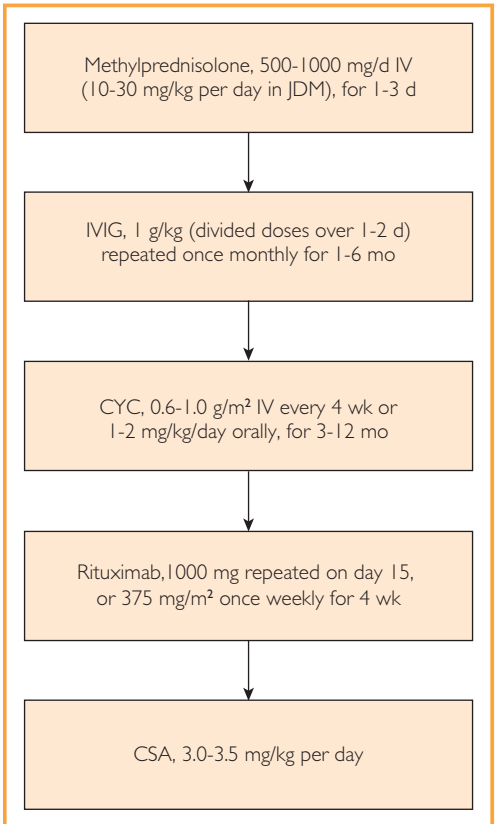

FIGURE 2. Treatment of idiopathic inflammatory myopathy refractory to conventional therapy or with severe organ-threatening manifestations such as interstitial lung disease, severe dysphagia with weight loss, severe weakness, or cardiomyopathy. CYC = cyclophosphamide; CSA = cyclosporine A; IV = intravenous; IVIG = intravenous immunoglobulin; JDM = juvenile dermatomyositis.

of 0.6 to 1.0 g/m^2 is given after adequate oral hydration (2-3 L within 24 hours) and intravenous hydration with normal saline, antiemetics, and mesna (40% of CYC dose). Oral mesna is given 4 and 8 hours after CYC infusion for 2 doses (20% of CYC infusion) to reduce the complication of hemorrhagic cystitis. Cyclophosphamide infusions are given every 4 weeks for 3 to 6 months. Infrequently, the duration is extended to 12 months. It is our practice to monitor the white blood cell count for the nadir that occurs 8 to 14 days after CYC infusion to avoid a nadir of less than 3.0 × 10(9)/L.[3] If CYC is given orally, we administer 1 to 2 mg/kg, but we do not exceed a 200-mg daily dosage. Patients are advised about maintaining adequate hydration to avoid hemorrhagic cystitis. We recommend that patients urinate frequently, especially first thing in the morning on waking, to prevent the acrolein metabolite from inducing hemorrhagic cystitis.

Rituximab is becoming the alternative to CYC in patients who have refractory IIM or severe disease complications. Rituximab is a human monoclonal antibody to CD20 that is expressed on B cells and depletes circulating B cells. Levine[119] performed an open-label trial of 6 patients with DM who received 4 weekly infusions at 375 mg/m^2 and found improvement in muscle strength, reduction of CK levels, and improved cutaneous and pulmonary disease after 12 weeks. Myositis seemed to recur when circulating B cells returned. Mahler et al[120] conducted a prospective trial in 13 patients with refractory IIM to assess the efficacy of rituximab dosed at 1000 mg in a 2-week interval and found a significant reduction in muscle enzyme levels and improvements in strength, disease activity, and quality of life scores at 27.1 months of follow-up. The Rituximab in Myositis study,[121] the first prospective, double-blind, randomized, multicenter trial of rituximab in myositis, involved 200 pediatric and adult patients who received rituximab for refractory disease. A favorable response and improvement was seen in 83% of patients throughout the 44-week trial. We administer two 1000-mg doses of rituximab 2 weeks apart for adults. We obtain baseline immunoglobulin levels (IgG, IgM, IgA), determine hepatitis B and C antibody levels, and screen for latent tuberculosis prior to administering rituximab. Severe infectious complications are a concern. Progressive multifocal leukoencephalopathy has been reported in rheumatic patients treated with rituximab; caution should be used in patients who are severely immunosuppressed.[122] Progressive multifocal leukoencephalopathy also has been reported in patients with myositis who have not been treated with rituximab; therefore, a high index of suspicion for JC virus reactivation should be reserved for any patient presenting with central nervous system abnormalities.[123]

Cyclosporine A (CSA) and tacrolimus are agents that inhibit T-cell–mediated immune functions such as suppression of IL-2 gene transcription. They have been used for the

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treatment of IIM with severe ILD. In one open-label, randomized study,[124] 36 patients with active DM or PM were randomized to either MTX at dosages of 7.5 mg to 15 mg once weekly or CSA at dosages of 3.0 to 3.5 mg/kg daily. The 2 groups had equal improvement in outcomes such as strength, endurance, and patient global assessments. Additionally, a few retrospective trials of CSA have demonstrated improvement in ILD and partial regression of calcinosis; however, because of serious adverse effects including hypertension and renal insufficiency, the use of CSA is limited.[125,126] Serum CSA trough levels are monitored routinely to avoid renal toxicity. Oddis et al[127] described pulmonary improvement in 8 patients with IIM treated with tacrolimus who had anti-Jo-1 or anti-SRP antibodies. Due to concern about serious adverse effects, our practice is to reserve the use of CSA and tacrolimus for severe, refractory IIM.

Initial Treatment Approach to Patients With JDM

For children with JDM, we begin prednisone at 2 mg/kg up to a maximum of 60 mg/d with a taper after 2 to 4 weeks depending on patient response, similar to the corticosteroid taper for adult patients with myositis. A suggested corticosteroid taper schedule was recently published by Huber et al[128] based on consensus-driven treatments: reduce corticosteroid dosages of 2 mg/kg every 2 weeks until the dosage reaches 0.5 mg/kg and then taper the dosage by 10% to 20% of the current dosage for 4 weeks until completion. Subcutaneous MTX is added at the onset at a dose of 15 mg/m^2 once weekly and is a key component of the Childhood Arthritis and Rheumatology Research Alliance consensus treatments.[129]

Treatment Approach to Patients With JDM Refractory to Standard Treatment

For patients with JDM who present with severe muscular and/or extramuscular disease or disease refractory to standard treatment, we administer IVMP at 30 mg/kg to a maximum of 1 g/d for 3 days. Several small trials have described improvement in outcomes with IVMP, usually in conjunction with MTX and/or hydroxychloroquine. Huang[130] conducted a retrospective study of 24 patients with JDM and found that 13 of 24 patients treated with IVMP initially had a shorter time to achieve normal strength and improvement of rash. Al-Mayouf et al[131] studied 12 patients with severe JDM with dysphagia and/or cutaneous vasculitis treated with MTX and IVMP early in the disease course or 5 to 72 months after diagnosis. All 6 patients treated early with MTX improved and achieved discontinuation of corticosteroids and remission without development of calcinosis. Riley et al[132] used intravenous CYC at dosages of 0.5 to 1.0 mg/m^2 to treat JDM, and 10 of 12 patients had disease improvement. Intravenous immunoglobulin is also efficacious (and safe) in JDM, as proven in 38 children treated with 1056 infusions; adverse events were reported in preparations containing high IgA levels.[133] Other immunosuppressive drugs have been used such as azathioprine, CSA, and systemic tacrolimus.[134-136] Mycophenolate mofetil is not routinely used as a conventional immunosuppressant in children with JDM, although one report described a case series of MMF use at a dosage range from 800 to 1350 mg/m^2 per day in 8 children with JDM that resulted in improved muscle strength and ability to taper corticosteroids by at least 18% after 3 months of therapy.[137] Finally, rituximab is gaining acceptance for treating severe or refractory JDM. Bader-Meunier et al[138] conducted a multicenter trial of 9 patients with refractory JDM and found that 3 of 6 children treated with rituximab for severe muscle disease had complete clinical remission; they were able to taper the corticosteroids to less than 15% of the child's baseline dosage or stop corticosteroids completely after a follow-up of 1.3 to 3 years. If rituximab is chosen to treat JDM, we use the following doses: children with a body surface area of 1.5 m^2 or less receive 575 mg/m^2 at each infusion, and children with a body surface area greater than 1.5 m^2 receive 750 mg/m^2 up to 1 g per infusion.

Therapy for Skin Disease in DM and JDM

Avoidance of UV rays is paramount to preventing skin flares in patients with DM and JDM; judicious use of sunscreens with a sun protection factor of 50 or higher in addition to appropriate coverage with wide-brimmed hats and long-sleeved shirts should be advised. Topical corticosteroids at varying strengths as well as topical tacrolimus (0.1%) has been used in JDM and DM.[139]

Hydroxychloroquine is an antimalarial drug administered at 200 mg twice daily (5 mg/kg). It is primarily used for cutaneous manifestations of DM or JDM. For nonresponders, chloroquine can be used at dosages of 250 to 500 mg/d. A baseline electrocardiogram should be obtained to screen for QT prolongation. Quinacrine is another treatment option.[87] Ophthalmologic monitoring for retinal toxicity using newer testing modalities such as multifocal electroretinography and spectral domain optical coherence tomography is important before drug initiation as a baseline screening to rule out macular disease; subsequent annual screening should begin 5 years or less after initiation of the drug if the patient is still taking hydroxychloroquine and there are underlying risk factors for retinal toxicity.[140] For refractory skin disease, MMF has been reported to be effective.[110,111] Intravenous immunoglobulin may be helpful as an additional medication for treatment of refractory skin disease.[87,114]

Treatment of Calcinosis in DM and JDM

Calcinosis cutis is a common complication of JDM, and its presence suggests active disease in JDM and a delay to diagnosis and treatment.[141] Classically, calcinosis is found at the subcutaneous level, but it may be seen intramuscularly, in fascial planes, and in areas at risk for trauma such as the elbows and knees. Calcinosis may also be present in adult patients with DM and those with DM/scleroderma overlap, although it is less common than in JDM. Calcinosis is discouraging to treat because of the lack of meaningful response with most treatments. Several agents have been used with minimal or no improvement, including diltiazem, colchicine, bisphosphonates, probenecid, warfarin, and intralesional corticosteroids. Of these agents, diltiazem may produce a partial response.[142] However, a recent case report noted improvement of severe ulcerative skin disease and calcinosis with abatacept and sodium thiosulfate, a vasodilator that chelates calcium, in a 14-year-old girl with recalcitrant JDM, although use of these medications would be off label in this context.[143] Eventually, the calcinosis may regress, although joint contractures and secondary infections may be complications. If there is considerable pain associated with an area of calcinosis, surgical excision may be an option.

Treatment of sIBM

In general, we treat patients with newly diagnosed sIBM with immunosuppression using the same treatment algorithms used for DM and PM with the goal of suppressing muscle inflammation, although the disease typically is resistant to standard immunotherapy. The rationale for immunotherapy is that early suppression of the inflammatory cascade may prevent downstream effects leading to muscle degeneration by interfering with protein misfolding.[144] However, the degenerative process may predominate over time, leading to loss of efficacy with conventional immunosuppression. If the patient has severe dysphagia, IVIG may be efficacious, although there may be loss of therapeutic benefit over time.[145-147]

Unfortunately, most treatment trials involving patients with sIBM have been small and yielded little with respect to improved outcomes in strength and muscle mass. A randomized, placebo-controlled trial using anti−T-lymphocyte globulin therapy demonstrated improvement in mean muscle strength (1.4%) in 6 patients treated for 12 months compared with patients treated with MTX.[148] Another small pilot trial using oxandrolone showed borderline significant improvement in upper extremity muscle strength in patients with sIBM.[149] Two small randomized, placebo-controlled trials used interferon-β-1a (βINF1a) as treatment.[150,151] One study was a 24-week multicenter trial assessing the safety and tolerability of βINF1a with a secondary goal of measuring improvements in strength and muscle mass; however, no differences were found between placebo and treated groups at 6 months, and 2 patients experienced severe adverse events including death.[150] The second study investigated the tolerability of a higher dose of βINF1a and found no difference in strength and mass compared with placebo.[151] Dalakas et al[152] examined the effect of the monoclonal antibody alemtuzumab (Campath-1H), a medication that depletes peripheral lymphocytes, in 13 patients with sIBM treated for 4 days and found that the decline in strength had lessened 6 months after therapy along with some improvement in ADLs.

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TREATMENT RESPONSE

Patient response to treatment depends on several factors including tolerance to therapy, the severity of the muscle disease, and the extent and severity of extramuscular organ involvement, if present. In general, we measure improvement of disease by muscle strength based on the manual muscle test (MMT), serum muscle enzyme level normalization at successive clinic visits, the patient's physical function as determined by validated questionnaires, patient and physician global assessment of disease activity, and physician assessment of improvement of extramuscular organ involvement (Table 2).[153,154]

TABLE 2. Core Measures for Assessment of Disease Activity in Inflammatory Myositis (Adult and Juvenile)

Domain	Core set measures
Global activity	Physician global disease activity assessed by Likert or VAS; patient/parent global disease activity assessed by Likert or VAS
Muscle strength	Manual muscle strength testing to include proximal, distal, and axial muscles
Physical function	For adults, validated ADL questionnaire (HAQ, MAP) For children ≥4 y, validated ADL questionnaire (CHAQ) For children <4 y, validated ADL questionnaire (CHAQ) and observational tool of function, strength, and endurance (CMAS)
Laboratory assessment	At least 2 serum muscle enzyme measurements from the following: CK, aldolase, LDH, AST, or ALT
Extramuscular disease	Validated approach assessing cutaneous, gastrointestinal, joint, cardiac, and pulmonary activity

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHAQ = Childhood Assessment Health Questionnaire; CK = creatine kinase; CMAS = Childhood Myositis Assessment Scale; HAQ = Health Assessment Questionnaire; LDH = lactate dehydrogenase; MAP = Myositis Activities Profile; VAS = visual analog scale.
Adapted from *Rheumatology (Oxford)*,[154] with permission from Oxford University Press.

Disease Assessments

There are several instruments, mostly organ-specific but also involving quality of life and function, that are used to assess disease status and response to therapy. Two international collaborative groups, the International Myositis Assessment and Clinical Studies Group and the Paediatric Rheumatology International Trials Organisation, have recommended a core set of measures to assess disease activity, disease damage, and quality of life in adults and children.[46,153,154]

Global Activity. Overall disease activity based on the patient's history, physical examination findings, laboratory results, and medical therapy is rated on a 10-cm visual analog scale, although a 5-point Likert scale may be used at the time of a patient visit. Patients or parents of patients record the extent of disease activity involving all affected organs that can improve with treatment. The Likert scale is scored with 0 indicating no disease activity and 4 indicating severe disease activity. On the visual analog scale, a score of 0 to 10 decimal places is used with higher score indicating severe disease activity[153,154] (Table 2).

Skin. Skin disease may correlate with disease activity, disease damage, and physical function in patients with JDM and DM; hence, assessment of cutaneous activity is important to disease management.[86] The Cutaneous Assessment Tool is a comprehensive tool assessing skin disease in JDM and adult DM that involves "activity lesions" such as Gottron papules, shawl sign, and ulcerations and "damage lesions" such as atrophy and/or hypopigmentation/hyperpigmentation in the distribution of a previous Gottron papule, heliotrope rash, or lipoatrophy using a weighted scale to determine severity.[155,156] Other tools used to assess skin disease in adults include the Dermatomyositis Skin Severity Index and the Cutaneous Dermatomyositis Disease Area and Severity Index.[157,158]

Muscle. The manual muscle test is used to measure muscle strength, reported as a score of the number of proximal, distal, and axial muscle groups tested on both sides (26 muscle groups).[153,154,159] The MMT has been shortened to MMT8 that scores the 8 proximal, distal, and axial muscle groups on one side.[153,159] The United Kingdom Medical Research Council System scale (0-5) is commonly used to gauge muscle strength: 0 indicates the lowest strength and 5 the highest.[160] We commonly test muscle groups bilaterally: neck flexion/extension, shoulder abduction, elbow flexion/extension, wrist flexion/extension, hip flexion/extension, hip abduction/adduction, knee flexion/extension, ankle dorsiflexion, and plantar flexion.

Physical and Occupational Function. There are several outcome measures to assess ADLs in

patients with IIM. The International Myositis Assessment and Clinical Studies group has established a core set of measures for assessment of IIM[153,154] (Table 2). The Stanford Health Assessment Questionnaire (HAQ) is a self-survey of ADLs. Although not specific for IIM, the Stanford HAQ assesses diminished physical function in the following domains: dressing and grooming, standing up, eating, personal hygiene, walking, reaching, gripping, and activities. The score range is 0 to 3.0, with disability graded in the following manner: 0.1 to 1.0, mild disability; 1.01 to 2.0, moderate disability; and 2.01 to 3.0, severe disability.[161] The Myositis Activities Profile is a recently validated assessment measure of myositis-specific ADLs in the following domains: movement, activities of moving around, personal care and hygiene, household work, social activity, avoiding overexertion, work/schoolwork, and recreation.[162,163]

Assessment of muscle endurance and stamina is obtained with the Functional Index-2, which measures repetitions in 7 muscle groups: shoulder flexion, shoulder abduction, neck flexion, hip flexion, knee extension, heel lifts, and toe lifts. Scores range from 0 to 60 for shoulder flexion, shoulder abduction, neck flexion, hip flexion, and step test tasks and from 0 to 120 for heel and toe lifts.[164] The Functional Index-2 is a modification of the original Functional Index in Myositis, which is an assessment tool for muscle impairment in patients with DM and PM.[165]

Assessment in JDM involves the use of several outcome measures. The Childhood Myositis Assessment Scale is a validated tool that assesses muscle strength, endurance, and functional capacity in juvenile IIM.[166,167] The Childhood HAQ is also a validated instrument to assess limitations in ADLs in children with JDM; similar to the adult HAQ, it focuses on 8 domains: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities.[166,168]

Assessment of sIBM involves the Inclusion Body Myositis Functional Rating Scale, which is a validated 10-point disease-specific functional scale rating specific tasks. These tasks include swallowing, handwriting, handling utensils and cutting food, fine motor tasks, dressing, standing, walking, hygiene (bathing and toileting), turning in bed and adjusting covers, moving from sitting to standing positions, and climbing stairs.[169] It is a modification of the Amyotrophic Lateral Sclerosis Functional Rating Scale, which was originally developed to assess ADLs in patients with amyotrophic lateral sclerosis and was later revised to include respiratory function.[170,171]

Physical Therapy

In general, patients with DM, PM, or JDM may regain full or partial physical function after adequate treatment. Physical therapy should be instituted early in the course of the muscle disease to avoid joint contractures and muscle atrophy that can occur from disuse. Goals of therapy should be to regain muscle strength and function. Patients should meet regularly with a therapist to embark on a routine that incorporates both stretching and strengthening activities because exercise may have downstream effects in improving muscle inflammation.[172] Alexanderson et al[173] found that intensive resistance training was beneficial and safe in 9 patients with DM or PM who exercised 3 days per week for 7 weeks without worsening of muscle disease. However, patients with sIBM eventually may become severely disabled. Referral to a physiatrist is essential early in the sIBM disease course to determine whether assistive devices are needed. Referral to a speech pathologist is important to educate patients on appropriate swallowing techniques.

Novel Biomarkers of Disease Activity

Muscle enzyme levels and results of muscle strength testing may not always be an accurate reflection of disease activity in DM or JDM, especially if the muscle tissue is affected by chronic fibrosis and atrophy.[13] Emerging studies using gene expression profiling of peripheral blood cells and muscle tissue suggest that IIM has immune "fingerprints" that may be useful in monitoring disease activity and treatment response.[35-39] Potential biomarkers of disease activity in DM and JDM have been identified, in particular the proinflammatory cytokine IL-6 and type 1 interferon–regulated genes. Interleukin 6 helps regulate the innate and adaptive immune responses, promotes tissue inflammation, and has both B- and T-cell differentiation activity.[174,175] Type 1 interferon may play a role in the pathogenesis of DM, akin to

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the pathogenesis model of human systemic lupus erythematosus.[176,177] Type 1 interferons are important in up-regulating MHC class I expression, promoting activated T cells, activating natural killer cells, and influencing dendritic cell maturation.[35,178] A recent study by Baechler et al[36] found that a type 1 interferon signature in the peripheral blood of patients with DM may correlate with disease activity, suggesting its usefulness in monitoring disease activity. Similarly, Bilgic et al[35] found that type 1 interferon genes and IL-6 may be biomarkers of disease activity in adult DM and JDM. Recently, Reed et al[39] prospectively evaluated patients with DM and JDM and their type 1 interferon peripheral blood gene "scores" and chemokine signatures. They found that disease changes in DM and JDM, before and after treatment, positively correlated with the type 1 interferon gene score. Moreover, serum levels of proinflammatory cytokines, IL-6, IL-8, and TNF-α positively correlated with changes in muscle disease activity, suggesting that they may be sensitive biomarkers of disease activity. However, the feasibility of obtaining these biomarkers in clinical practice has not yet been demonstrated.

Secondary Prevention of Corticosteroid Adverse Effects

Because of the prolonged use of corticosteroids in patients with IIM, we recommend that patients' bone health be monitored with routine dual-energy x-ray absorptiometry. We prescribe calcium and vitamin D supplements, and if osteoporosis is evident, a bisphosphonate is prescribed. In addition, we use *Pneumocystis* prophylaxis such as trimethoprim-sulfamethoxazole if the patient is taking 20 mg or more of corticosteroids for 4 weeks or longer, although there are no consensus guidelines for prophylactic regimens in non—human immunodeficiency virus-infected rheumatic patients to date.[179,180]

Pitfalls of Treatment

Corticosteroid Adverse Effects. Unfortunately, studies of long-term outcomes in IIM have shown that corticosteroids are a major cause of morbidity. The primary adverse outcomes are osteoporosis, compression fractures, and avascular necrosis.[181] Other common complications of long-term corticosteroid use include excessive weight gain, hypertension, stretch marks, growth delay in children, cataracts, diabetes, dyslipidemia, and corticosteroid-induced myopathy.

Infection Risks. Immunosuppressants are associated with an increased risk of serious nonopportunistic and opportunistic infections. Patients who take these drugs become susceptible to upper respiratory tract infections, serious pneumonias, skin infections, bacteremia, and sepsis and have an increased risk for death. Patients with comorbidities such as diabetes, chronic liver disease, chronic kidney disease, or organ transplant are likely to experience infectious complications. Vaccines should be updated before beginning any immunosuppressants. These vaccines should include the pneumococcal, influenza (intramuscular), hepatitis B, and recombinant human papillomavirus for cervical cancer vaccines and live attenuated herpes zoster vaccine for shingles.[182] Live vaccines generally are contraindicated in patients already taking immunosuppressants, especially those who are taking an anti-TNF biologic agent or a non-TNF biologic agent such as rituximab because of the theoretical risk of infection from vaccination in this group. However, the Centers for Disease Control and Prevention recommends that patients who are taking less than 20 mg of prednisone daily and MTX or azathioprine at doses used for rheumatic disease may receive the shingles vaccine.[183]

CONCLUSION

The management of IIM involves goals of eliminating organ inflammation and preventing disease complications to reduce morbidity and restore quality of life. Unfortunately, there is a paucity of large-scale, randomized controlled trials to guide treatment decisions and provide information on long-term outcomes in patients with IIM. Much of the treatment advice is based on expert opinion. Our institution has a standard protocol for the workup and treatment of patients with IIM. Myositis-specific autoantibodies have become useful in defining clinical subsets of IIM and suggesting a prognosis. Magnetic resonance imaging is useful in diagnosing myositis and following treatment response. Our treatment approach for newly diagnosed uncomplicated IIM is to initiate high-dose corticosteroids at diagnosis

concurrent with MTX, azathioprine, or MMF. For adult and juvenile patients with severe myositis, we administer high-dose methylprednisolone in addition to IVIG, CYC, rituximab, or cyclosporine. Several trials are under way involving new medications to treat patients with myositis. Moreover, emerging research suggests that type 1 interferon genes, IL-6 levels, and other proinflammatory cytokines may potentially serve as indicators of disease activity and treatment response.

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Abbreviations and Acronyms: **ADL** = activities of daily living; **βINF1a** = interferon-β-1a; **CK** = creatine kinase; **CSA** = cyclosporine A; **CT** = computed tomography; **CYC** = cyclophosphamide; **DM** = dermatomyositis; **EMG** = electromyography; **HAQ** = Health Assessment Questionnaire; **HMGCR** = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; **IIM** = idiopathic inflammatory myopathy; **IL** = interleukin; **ILD** = interstitial lung disease; **IMNM** = immune-mediated necrotizing myopathy; **IVIG** = intravenous immunoglobulin; **IVMP** = intravenous methylprednisolone; **JDM** = juvenile dermatomyositis; **MHC** = major histocompatibility complex; **MMF** = mycophenolate mofetil; **MMT** = manual muscle test; **MRI** = magnetic resonance imaging; **MSA** = myositis-specific autoantibody; **MTX** = methotrexate; **pDC** = plasmacytoid dendritic cell; **PM** = polymyositis; **sIBM** = sporadic inclusion body myositis; **TNF-α** = tumor necrosis factor α; **tRNA** = transfer RNA

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