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Developments in the Classification and Treatment of the Juvenile Idiopathic Inflammatory Myopathies

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Abstract

The juvenile idiopathic inflammatory myopathies (JIIM) are rare, heterogeneous autoimmune diseases that share chronic muscle inflammation and weakness. JIIM broadly includes three major clinicopathologic groups: juvenile dermatomyositis, juvenile polymyositis, and overlap myositis. A growing spectrum of clinicopathologic groups and serologic phenotypes defined by the presence of myositis-specific or myositis-associated autoantibodies are now recognized, each with differing demographics, clinical manifestations, laboratory findings, and prognoses. With the first multi-center collaborative studies and controlled trials using standardized preliminarily validated outcome measures, the therapy of juvenile myositis has advanced. Although daily oral corticosteroids remain the backbone of treatment, disease-modifying anti-rheumatic drugs (DMARDs) are almost always used as adjunctive therapy. Methotrexate is the conventional DMARD for the initial therapy, either alone or combined with intravenous pulse methylprednisolone, and/or intravenous immunoglobulin for patients with moderate to severe disease. Cyclosporine may be added to these or serve as an alternative to methotrexate. Other drugs and biologic therapies, including mycophenolate mofetil, tacrolimus, cyclophosphamide, rituximab, and infliximab, might benefit selected patients with recalcitrant disease, unacceptable steroid toxicity, or patients with risk factors for poor prognosis. The treatment of cutaneous disease, calcinosis, and the role for rehabilitation are also discussed.

Keywords

Juvenile myositis; juvenile dermatomyositis; juvenile polymyositis; overlap myositis; myositis specific autoantibodies; treatment; biologic therapies

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The juvenile idiopathic inflammatory myopathies (JIIM) are heterogeneous immune-mediated disorders characterized by chronic skeletal muscle inflammation, but often include characteristic skin rashes and involvement of other organs. The diagnosis of these conditions remains based on the clinical and laboratory criteria of Bohan and Peter ¹, with acknowledged limitations that many pediatric patients with characteristic rashes do not undergo electromyography or muscle biopsy ². These disorders can be classified based on clinicopathologic features or on the presence of autoantibodies found almost exclusively in myositis patients, known as the myositis autoantibodies. This sub-classification of JIIM assists in understanding patients who share demographic and clinical features, laboratory abnormalities, responses to therapy, and prognoses. We now present an update to our understanding of the classification of juvenile myositis from work first published more than 15 years ago ³ and an update on recent advances in the treatment of JIIM, reflecting collaborative multi-center studies and the introduction of biologic therapies for these diseases.

Clinicopathologic classification of JIIM

The recent classification has been achieved by large registry studies that have better defined the features of the most common phenotypes, and additional case series and reports that have enhanced our understanding of the spectrum of the rarer clinical phenotypes. The classification of JIIM, based on clinical and histologic features, has been recognized both in adults and children with myositis, with the finding that the same clinical subgroups exist in JIIM as adult IIM but with different relative frequencies and slight differences in manifestations and prognoses ^{4,5}. While JIIM is 5-fold less common than adult IIM, in children, dermatomyositis (DM) is the most frequent of the IIMs whereas polymyositis (PM) is relatively more frequent in adult IIM than in JIIM. Inclusion body myositis (IBM) and cancer-associated myositis are almost exclusively seen in adults. Since our first proposal of clinicopathologic groups for JIIM ³, several new forms of IIM have been recognized, including macrophagic myofasciitis and immune-mediated necrotizing myopathy ⁶, and the spectrum of amyopathic DM has expanded to include hypomyopathic DM (Table 1). Infantile polymyositis is no longer recognized as a subgroup of JIIM but was found to be a muscular dystrophy (laminin alpha2 or merosin deficiency) ⁷.

The most common clinical phenotype of myositis in children, constituting approximately 85% of all JIIM patients, is **juvenile dermatomyositis (JDM)**, which is characterized by symmetric proximal muscle weakness and the presence of characteristic rashes, i.e., Gottron's papules (erythematous plaques overlying the extensor joint surfaces) or heliotrope rash (a purplish or erythematous rash over the eyelids). One of the hallmarks of JDM, vasculopathy, is evident by examining the periungual capillaries, which are often dilated, tortuous, and decreased in density due to an immune-mediated attack, which is distinct from vasculitis. Several national registry studies have expanded our understanding of the clinical spectrum of JDM as a systemic autoimmune disease ^{5,8-11}. Patients with JDM have a median age of onset of 7.5 years, and in addition to the characteristic skin rashes, they have frequent malar rash, photosensitivity, linear extensor erythema, and other cutaneous findings. Their creatine kinase (CK) levels are elevated but they tend to be lower. Mortality is intermediate between JDM and overlap myositis ⁵. The prognosis of JDM is variable, with a low overall mortality of 2–3%, and approximately 24–40% of patients having a monocyclic course, recovering with appropriate therapy within a 2-year period ^{5,12}. However, the majority (50–60%) of patients with JDM experience a chronic illness course. Persistent periungual capillary abnormalities and active skin disease have been associated with a chronic illness course ^{12,13}. Patients with a chronic illness course and poor prognosis might also have cutaneous or gastrointestinal ulcerations, or less commonly pulmonary or

gastrointestinal tract air leaks (pneumomediastinum or pneumatosis intestinalis), indicating severe vasculopathy¹⁴. Calcinosis occurs in 20–40% of patients^{5;9;15}, with a lower prevalence in patients treated more aggressively who enter remission more rapidly¹⁶. Calcium and phosphate precipitate in the subcutaneous tissues and muscles as carbonate apatite, perhaps as a result of a loss of mineralization inhibitors¹⁷. Risk factors for calcinosis include delay to diagnosis, cardiac involvement, the need for additional immunosuppressive therapy, as well as a prolonged and/or severe illness course¹⁵. Another complication of JDM, lipodystrophy, occurs in up to 10% of JDM patients and is characterized by progressive loss of subcutaneous fat in a localized, partial (i.e., only in the extremities), or widespread distribution. Lipodystrophy has been associated with calcinosis, muscle atrophy, joint contractures, and facial rash and should be recognized early because of its association with metabolic sequelae of insulin resistance, diabetes, and hyperlipidemia, with frequencies proportionate to the degree of fat loss¹⁸.

Overlap myositis, in which patients meet the criteria for JIIM as well as another autoimmune disease, is the next most common clinical phenotype of JIIM, occurring in 6–11% of patients^{5;8}. Raynaud's phenomenon, interstitial lung disease, arthritis, and malar rash are more frequent illness features in this subgroup. Patients with overlap myositis are more likely to have JDM than JPM, more often have myositis-associated autoantibodies, and are more often non-white^{5;19}. Among the JIIM subgroups, overlap myositis has a relatively higher mortality rate, which is often related to lung disease^{5;20}. The most common overlapping autoimmune conditions include systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, and localized scleroderma⁵. Although organ-specific autoantibodies, including those for autoimmune thyroid disease and hepatitis, type I diabetes, and celiac disease, have been observed in 2–15% of patients with JDM, these autoantibodies were not accompanied by overt organ-specific overlapping autoimmune diseases in one population²¹.

Juvenile polymyositis (JPM), which is seen in about 4–8% of JIIM patients, is characterized by both proximal and distal muscle weakness, but lacks the characteristic rashes of JDM. The pathologic findings also differ from JDM, with frequent endomysial infiltrates in affected muscles^{5;8;10;22}. Patients with JPM tend to be older, with onset in pre-teen or teenage years, have higher CK levels, more myalgias, and more severe illness onset. They often have frequent falling episodes, a sign of distal weakness, and cardiac involvement occurs in approximately one third of JPM patients. Mortality is intermediate between JDM and overlap myositis⁵. A muscle biopsy is required for diagnosis, as JPM is often misdiagnosed in patients who actually have other non-inflammatory myopathies, particularly muscular dystrophies, which have more frequent myopathic features on biopsy and clinical muscle atrophy²³. JPM patients also frequently have myositis-specific and myositis-associated autoantibodies, particularly anti-aminoacyl tRNA synthetase (anti-synthetase) and anti-signal recognition particle (SRP) autoantibodies⁵.

The other clinicopathologic phenotypes of the JIIM are uncommon (Table 1). Of these, true **DM sine myositis**, without evidence of muscle involvement is rare. However, **hypomyopathic DM** is occasionally observed, in which DM skin rashes are present for at least 6 months in patients who have no detectable weakness, but have evidence of muscle inflammation on testing (including elevated serum muscle enzyme levels, or an abnormal electromyogram, muscle biopsy, or muscle magnetic resonance imaging [MRI]). A thorough review of 68 cases of juvenile-onset, clinically amyopathic DM, which encompasses both DM sine myositis and hypomyopathic DM, showed that 26% of subjects subsequently developed classic JDM and that this disease progression occurred up to several years later^{24;25}. At onset only 4% of those patients had an elevated CK level, and of those with a normal CK level, only a minority had an abnormal EMG, muscle biopsy, or MRI,

suggesting that these patients can be treated symptomatically for their cutaneous disease, with close clinical monitoring for progression to muscle involvement²⁴. Calcinosis was reported in only 4%, and none had ulcerations, interstitial lung disease, or malignancy²⁴, which are the manifestations that are often associated with amyopathic DM in adults²⁶. A case report noted cutaneous ulcerations and interstitial lung disease in a lethal case of juvenile clinically amyopathic DM²⁷. The outcome of hypomyopathic DM appears to be good; for example, in 24 patients, 65% recovered spontaneously without therapy, and 5 of 10 patients treated with systemic therapy entered remission²⁸.

Malignancy in association with JIIM is so uncommon that routine screening for cancer is generally not warranted. In contrast, adults with DM and PM routinely undergo malignancy screening due to an increased risk for malignancy within 2 years of myositis onset²⁹. Nevertheless, a tumor may present with an autoimmune, myositis-like picture in childhood³⁰. In a Brazilian registry of 189 patients with JIIM, there was an associated malignancy in 2 (1.1%) cases¹⁰, but in other large JIIM registry studies co-existing cancer was not reported^{5;8;9}. Atypical illness features, including prominent adenopathy, hepatosplenomegaly, palpable masses, and atypical rashes, have been proposed to be part of a profile of indicators that might indicate an underlying malignancy, in that at least one of those features was observed in the majority of the 17 reported cases of cancer in association with JIIM^{3;30;31}. The most common associated cancers in children have included lymphoma, leukemia, and solid organ tumors.

Focal myositis, alternatively termed an inflammatory “pseudotumor” or “focal nodular myositis,” is characterized by an often painful intramuscular swelling or mass in a single muscle group which develops over several weeks or months, sometimes preceded by trauma. The most common sites of involvement are the thigh muscle groups, gastrocnemius, brachialis, and sternocleidomastoid, but any muscle may be affected^{32;33}. This disorder must be distinguished from malignant tumors and infectious etiologies, including Lyme disease. Although typically an isolated phenomenon, it can be associated with other rheumatic diseases. Histologic changes include fibrosis and intramuscular inflammation, particularly infiltration of macrophages which are occasionally accompanied by prominent eosinophils and CD4+ lymphocytes. Cases with severe inflammation have elevated B cells and plasmacytoid dendritic cells³². Limited follow-up found spontaneous resolution in several cases, with immunosuppressive therapy or surgical resection used for refractory disease³². A higher CK level, erythrocyte sedimentation rate, or limb atrophy may signal an increased risk of recurrence or progression to multifocal IIM³³.

Macrophagic myofasciitis (MMF) is an inflammatory myopathy thought to be related to aluminum-adjunct vaccines. MMF often has an active lesion at the immunization site, and systemic symptoms include myalgias, arthralgias, muscle weakness, chronic fatigue, and fever³⁴. In children, additional features include hypotonia, motor delay with an inability to stand or walk, and failure to thrive^{35;36}. Scanning electron microscopy with energy dispersive spectroscopy has been used to detect aluminum in tissue specimens³⁷. Histologically, granulomas composed of periodic acid-Schiff–positive and CD68-positive macrophages are generally seen. Typically, vaccination predates the diagnosis by 2–12 months, but has been as long as 10 years prior³⁸. MMF often occurs in individuals who have genetic susceptibility, in particular the HLA-DRB1*01 allele.

Other clinicopathologic forms of JIIM are rare and are described in Table 1.

Serologic classification of JIIM

An alternative classification of the JIM is by the presence of myositis autoantibodies. Two classes of autoantibodies include myositis-specific autoantibodies (MSAs), which are present almost exclusively in patients with myositis, and myositis-associated autoantibodies (MAAs), which are present in patients with myositis and in patients with other autoimmune diseases (Table 2). As the recognition of myositis autoantibodies has increased recently, this has enabled the identification of a myositis autoantibody in approximately 70% of JIIM patients⁵. These myositis autoantibodies define more homogeneous groups of patients with similar clinical features, responses to therapy, and prognoses. Of the autoantibodies studied in both children and adults, generally the same myositis autoantibodies have been seen, although some of them differ in frequency between children and adults. For example, anti-p155/140 and anti-MJ autoantibodies seem to be more prevalent in JDM than adult DM; conversely, the anti-synthetase autoantibodies, which are seen in approximately 5% of JIIM patients, are present in 25–40% of adult IIM patients⁵. There are also many similarities in the clinical and demographic features, laboratory findings, and prognoses between JIIM and adult IIM patients with the same myositis autoantibodies³⁹. Myositis autoantibodies are most accurately detected by validated protein and RNA immunoprecipitation assays, with certain autoantibodies, particularly anti-p155/140 and anti-MJ requiring additional confirmation by reverse immunoprecipitation-immunoblotting or immunodepletion methods^{40;41}. A line-blot assay is almost as sensitive and specific as protein immunoprecipitation in detecting the traditional MSAs and MAAs⁴².

The most frequent MSAs in JIIM are anti-p155/140 and anti-MJ autoantibodies, and they are associated primarily with JDM³⁹. Anti-p155/140 autoantibodies have reactivity to transcriptional intermediary factor 1 (TIF-1) and are present in 23–30% of JIIM patients, particularly in those with JDM or overlap myositis with JDM. Anti-p155/140 autoantibodies are associated with extensive photosensitive skin rashes, including the characteristic rashes of JDM, malar rash, V- and shawl-sign rashes, and linear extensor erythema, as well as periungual capillary changes, skin ulceration, and generalized lipodystrophy^{18;39;41}. JIIM patients with anti-p155/140 autoantibodies frequently have a chronic illness course³⁹. In adult IIM patients, but not in JIIM patients, anti-p155/140 autoantibodies are frequently associated with cancer-associated myositis⁴³. Anti-MJ autoantibodies are present in 20–25% of JIIM patients and are seen primarily in patients with JDM who have frequent muscle cramps, dysphonia, joint contractures, and a monocyclic disease course^{39;44;45}. Patients with this autoantibody group have more severe illness, with one report finding a higher frequency of calcinosis⁴⁴, another report detailing frequent muscle atrophy⁴⁵, and a third report showing more frequent hospitalizations and increased frequency of gastrointestinal ulceration³⁹.

Of the traditional MSAs, anti-synthetase autoantibodies, which are present in < 5% of JIIM patients overall, are less frequent in JIIM than adult IIM. They are more often seen in patients with JPM or juvenile overlap myositis, with a frequency of 9% and 13%, respectively³⁹. Anti-Jo-1 autoantibodies are the most common of the anti-synthetase autoantibodies. As in adults, children with these autoantibodies also have frequent interstitial lung disease, arthritis, Raynaud's phenomenon, fevers, and mechanic's hands³⁹. Among the MSA phenotypes, this group also has the highest mortality rate, due to interstitial lung disease^{20;39}. Anti-SRP autoantibodies are seen primarily in African-American girls with severe JPM who have proximal and distal muscle weakness, frequent falling episodes, Raynaud's phenomenon, very high CK levels, wheelchair use, and a chronic illness course^{39;46}. Cardiac disease is also likely associated with these autoantibodies, and, similar to adult IIM patients with anti-SRP autoantibodies, their disease is refractory to many

therapies⁴⁶. Myonecrosis, consistent with an immune-mediated necrotizing myopathy, is characteristic of the muscle pathology⁴⁶.

Other MSAs and MAAs are described in Table 2. Anti-Mi-2 is a traditional MSA that is associated with JDM and its cutaneous features. Anti-CADM-140, which is associated with rapidly progressive interstitial lung disease, cutaneous ulcerations, and mucinous papules, and anti-SAE autoantibodies, have been described in JIIM patients only in case reports^{47–49}. Anti-200/100, an MSA that targets HMG-CoA reductase, is associated with an immune-mediated necrotizing myopathy that resembles PM in adult patients and is more frequent in patients who have taken statins; it has not yet been described in JIIM patients⁶.

MAAs, including anti-U1RNP, anti-Ro, anti-PM-Scl, and anti-Ku autoantibodies, are present in up to 15% of JIIM patients overall, but are more frequent in patients with overlap myositis^{5,19}. Relatively little is known about their associated clinical features in JIIM, and the limited clinical correlative information is based primarily on adult IIM cohorts^{133–138}. Individuals who have no identified MSAs or MAAs currently comprise approximately 28% of patients. Although disease in this subgroup appears to be mild, it is likely comprised of several currently unrecognized autoantibody phenotypes. The strength of the clinical associations and prognostic information from the MSAs suggest that serologic data are likely valuable in guiding therapy.

Treatment Approaches for Juvenile Dermatomyositis

The development of new therapies for the JIIM has been historically hampered not only by the rarity of these conditions, but also by a lack of common outcome measures and controlled clinical trials, and by vastly different approaches to therapy by geographic region and specialty. Important advances in the past decade should help provide a foundation for the development of new therapies for JIIM. Two large international clinical research consortia, the International Myositis Assessment and Clinical Studies Group (IMACS) and the Pediatric Rheumatology International Trials Organization (PRINTO), have developed and preliminarily validated core set measures of myositis disease activity and damage, as well as preliminary definitions of improvement to be used as endpoints for therapeutic trials^{50–52}. Ancillary measures to assess cutaneous disease activity, physical disability, and quality of life have also been developed⁵⁰. These measures, including assessment of muscle strength and physical function by manual muscle testing, the Childhood Myositis Assessment Scale, and the Child Health Assessment Questionnaire, as well as extra-muscular activity and global activity assessments, were readily adopted for use in clinical studies and trials, which resulted in standardized outcome assessment and an improved ability to monitor responses to therapies. The first large randomized controlled trials of treatments for JDM have recently been conducted, including the first use of targeted biologic therapies^{53,54}. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) has developed consensus guidelines for the treatment of moderately active patients and for corticosteroid dose reduction⁵⁵, which help greatly to standardize care of patients.

The following discussion of therapy will emphasize three aspects of the current state of treatment for JDM, including new aspects of the initial treatment, drug and biologic therapies for refractory patients (Table 3), and treatment of cutaneous disease, calcinosis, and rehabilitation. Most of the therapeutic experience in the JIIM is related to studies and trials in JDM. Although these therapies are applicable to other forms of JIIM, the sequence and use of these medications differs slightly among the clinical and serologic phenotypes, and therapy for other JIIM phenotypes is often best directed from adult IIM studies⁵⁶.

The goals of therapy include elimination of active disease, which may result from inflammation (including type I interferons and pro-inflammatory cytokines), from vasculopathy, or from myogenic factors, such as endoplasmic reticular stress responses⁵⁷; and prevention of disease damage to muscle and other organ systems in order to reduce morbidity, while minimizing the side effects of medication^{9;58}. Aggressive initial treatment of JDM disease activity is thought to be essential in preventing the development of calcinosis. This is based on observations that, among patients who have received long-term high-dose corticosteroids, including intravenous pulse methylprednisolone (IVMP) therapy, or who were treated with multiple immunosuppressive therapies, fewer developed calcinosis and most of them more readily entered remission^{16;59}. Complete and rapid treatment of underlying inflammation is thought to be essential not only to fully restore muscle function, but also to prevent damage, including scarring and atrophy in the muscle and skin, to shorten the illness course, and to reduce or prevent calcinosis^{12;13}. Cutaneous activity, including panniculitis, is a risk factor for the development of calcinosis and lipodystrophy¹⁸ and thus requires attention in therapy. New biomarkers of disease activity, which include evaluation of the vasculopathy and immune activation⁶⁰ and the use of MRI can aide in the assessment of occult active disease and muscle damage.

Initial therapy

Current practice among pediatric rheumatologists for the treatment of JDM has been summarized in several recent publications^{11;61;62}. Daily oral corticosteroid therapy is universally utilized in the care of these patients. Stringer et al⁶¹ surveyed more than 160 North American pediatric rheumatologists and found that corticosteroid doses vary based on disease severity; nonetheless, an initial dose of prednisone at 2 mg/kg/day was preferred by over half the respondents, and dosages tend to remain higher in severe cases. Use of IVMP is common, particularly for moderate and severe patients, with a trend to deliver 3 to 5 daily doses of 30 mg/kg initially, followed by intermittent subsequent doses, particularly for severe disease. Almost 90% of respondents favored the use of corticosteroids in combination with a disease-modifying anti-rheumatic drug (DMARD), most commonly methotrexate. Hydroxychloroquine is used mostly for mild disease and cases with predominantly cutaneous manifestations, and cyclophosphamide was preferred for ulcerative cases (45%) or for lung involvement. Intravenous immunoglobulin (IVIG) was utilized to treat severe or refractory patients or those with predominant skin disease. A large PRINTO study of 145 recent-onset JDM patients and 130 patients experiencing a disease flare⁶², found that patients in North and South America more frequently received intravenous pulse corticosteroids at the beginning of illness compared to patients in Europe (59–74% vs. 19–38%). The use of methotrexate was similar throughout these regions, but cyclosporine and IVIG were favored in Europe for patients experiencing illness flares (16–40%). Guseinova et al conducted one of the largest retrospective reviews on treatment practice, involving 490 JIIM patients receiving care at 27 pediatric rheumatology centers in Europe and South America from 1980 to 2004¹¹. They found that methotrexate and IVMP were used in approximately 50% of patients, antimalarials in 32%, cyclosporine in 25%, and IVIG in 17%. Whereas treatment with high-dose IVMP, in combination with a DMARD, such as cyclosporine, cyclophosphamide, or azathioprine, was common in European centers, methotrexate and antimalarial medications were preferred by South American providers.

Recently CARRA developed consensus protocols to optimize the initial therapy of patients with moderately severe JDM^{55;63}. Three consensus treatment protocols have been proposed; given the risks of poorer outcomes for untreated or longstanding disease, as discussed above, as well as adverse effects of high-dose, long-term corticosteroid use⁶⁴, all three options propose combinations of therapies from the time of diagnosis. Use of steroids (2 mg/kg/day) and methotrexate (15 mg/m² or 1 mg/kg/dose) is common to all three

treatment arms, with 2 other arms adding IVMP (30 mg/kg, max 1 gram; 3 days in a row then optional once weekly) or IVMP with IVIG (2 g/kg every 2 weeks x3, then monthly). The early use of IVMP and other parenteral therapies is done in part to overcome the poor absorption of oral corticosteroids due to underlying vasculopathy⁶⁵ and to diminish disease activity more rapidly so as to potentially improve outcomes^{12;13;16;59}. Early introduction of corticosteroid-sparing medications, such as methotrexate, may also decrease the frequency of corticosteroid toxicity, including excessive weight gain, decreased growth velocity, and cataracts⁶⁴. CARRA is currently conducting prospective studies of these three treatment protocols. This treatment consensus represents an important advance, by considering steroid-sparing agents as part of the initial therapy of JDM and including multiple agents simultaneously as part of the initial therapy for some patients with high levels of disease activity or serious illness manifestations. A follow-up consensus report from the CARRA pediatric rheumatologists determined that patients with clinical improvement may undergo corticosteroid dose reduction every 2 weeks, or monthly for lower steroid doses, such that steroids would be discontinued by 10–12 months after diagnosis. Importantly, the criteria for reducing corticosteroid therapy include improvement or normalization of muscle strength, muscle enzymes, skin rashes, and other disease manifestations, emphasizing that all aspects of disease activity must be completely treated before therapy is further reduced or discontinued⁶³.

A recent large multi-center randomized controlled trial by PRINTO of 139 patients with newly diagnosed JDM demonstrated a trend toward greater response to therapy at 6 months when prednisone and methotrexate (74%) were used compared to prednisone and cyclosporine (67%) or prednisone alone (52%)⁵⁴. Time to inactive disease was significantly shorter and time to major therapeutic changes was significantly longer in the combination groups (prednisone with cyclosporine or methotrexate) compared to prednisone alone. The number of adverse events was highest in the group treated with cyclosporine (51%) compared to methotrexate (28%) or prednisone alone (21%). This first large randomized controlled trial for the initial treatment of JDM suggests that combination of prednisone with methotrexate or cyclosporine is more effective than prednisone alone, but the safety profile favors the use of methotrexate over cyclosporine.

Treatment of refractory disease

The use of other therapies to treat refractory disease is appropriate in patients with unacceptable medication toxicity and in patients with severe disease activity, with certain severe illness manifestations (such as interstitial lung disease, cutaneous or gastrointestinal ulcerations), or with a poor prognosis (such as the presence of anti-synthetase or anti-SRP autoantibodies). The use of IVIG to treat JDM was initially inspired by a double-blind, placebo-controlled trial in adult DM⁶⁶ and small case series or anecdotal reports in JDM³. Lam et al⁶⁷ published a retrospective review of their experience using monthly IVIG infusions in 30 JDM patients who failed initial therapy compared to 48 patients who did not go on to receive IVIG. The comparison of treatment outcomes was confounded for the IVIG group, which consisted of patients with more severe disease activity and included two subgroups of patients, namely, steroid-resistant patients (who failed to respond to 6 weeks of initial therapy with corticosteroids often with methotrexate or who had severe disease with dysphagia and marked weakness that required initial treatment with IVIG) and steroid-dependent patients (who improved with the initial 6 weeks of treatment but flared after subsequent dose reduction of corticosteroids). The IVIG group, particularly the steroid-resistant subgroup, achieved lower disease activity 30 days to 4 years after treatment compared to the corticosteroid-only group, based on analyses that used bias-reduction methods. Although IVIG infusions were generally tolerated well and most patients remained on IVIG for more than 2 years, IVIG preparations containing a high level of IgA were more

frequently associated with fever, malaise, nausea, and vomiting⁶⁸. IVIG may also be used in the initial treatment of JDM patients with moderately severe disease, as discussed above⁵⁵, including patients with severe weakness or dysphagia, ulcerative disease, or calcinosis³.

Mycophenolate mofetil is one of the few medications that have been studied formally in children with JDM, albeit in a small retrospective case series involving 50 children. That study demonstrated the efficacy of 12 months of therapy in refractory patients who had an average disease duration of 3.6 years. Skin and muscle activity steadily improved in most patients, based on a significant reduction in their Disease Activity Scores. Those who responded to mycophenolate mofetil also tolerated steroid dose reduction, with a mean decrease of 0.2 mg/kg/day. The most common adverse event was minor infection (upper respiratory, sinusitis, and otitis media), with a similar rate of infection in the first 6 months of therapy as in the months prior to initiation of mycophenolate mofetil. Similar observations were reported by Dagher et al⁶⁹ in 8 children with refractory JDM who received mycophenolate mofetil (800–1350 mg/m²/day) along with oral corticosteroids. There was improvement in Childhood Myositis Assessment Scale (CMAS) and manual muscle testing scores, as well as a decrease in daily steroid dose by an average of 18%. Rashes resolved in 2 patients, and calcinosis improved in 1 patient. Mycophenolate mofetil was tolerated well, except in one case with transient neutropenia.

Other treatments have been reported to be beneficial for specific types of patients. Oral tacrolimus, which has been beneficial in adult DM/PM patients with refractory disease, particularly in patients with interstitial lung disease and anti-synthetase or anti-SRP autoantibodies⁷⁰, has been reported to be beneficial for a few patients with refractory JDM, particularly those with cutaneous disease, enabling them to reduce their corticosteroid dose⁷¹. Intravenous pulse cyclophosphamide therapy (0.5–1 g/m² monthly for 6–14 doses) was used in 12 patients with cutaneous or gastrointestinal ulceration or other signs of vasculitis, interstitial lung disease, and/or extremely refractory disease⁷². Although 2 patients died, the remaining 10 patients who received a full course of therapy had significant improvement in muscle strength and function, skin and extramuscular disease activity, and serum levels of lactate dehydrogenase. Clinical improvement continued or was maintained for 6 months to 7 years after discontinuation of cyclophosphamide. The primary adverse events were reversible lymphopenia, *Herpes zoster* infection, and alopecia. In London, at the Great Ormond Street Hospital, similar success was preliminarily reported in a larger series of 56 patients for whom cyclophosphamide pulse therapy was used⁷³. In addition, calcinosis improved in 9 of 14 patients (64%).

The use of adrenocorticotrophic hormone (ACTH) gel administered subcutaneously (80 IU once or twice weekly) in 5 adult treatment-refractory DM patients, including one adult with JDM, resulted in moderately improved muscle strength, physical function, and skin rashes and decreased pain over 12 weeks⁷⁴. ACTH gel is the only FDA-approved medication for the treatment of myositis. While additional studies in adults will clarify its safety and effectiveness, ACTH gel could be used in selected treatment-refractory patients who are having trouble with absorption of oral corticosteroids due to vasculopathy⁶⁵, in patients who are non-compliant with oral medications, and as a bridge medication for a brief period.

Biologic therapies

Several open-label studies, case reports, and small trials have been recently completed that provide initial insights into the role of biologic therapies to treat refractory JDM. Rituximab depletes CD20+ B cells, which are elevated in the peripheral blood and muscle of patients with active disease, and might also diminish the production of myositis autoantibodies. Rituximab demonstrated early promise in open-label trials and case reports, with > 70% of treatment-refractory patients improving clinically⁷⁵. In an early report, 3 of 4 treatment-

refractory JDM patients entered remission after rituximab administration for up to 12–14 months⁷⁶. A review of rituximab use in 12 treatment-refractory JDM patients (most received rituximab weekly at a dose of 375 mg/m² for 4 weeks) found that 9 patients (75%) had improved muscle or cutaneous disease activity, and 5 (42%) achieved remission for up to 20 months⁷⁷. However, an open-label trial of rituximab in 8 adult patients with refractory DM showed 3 patients improved their muscle strength at week 24, but there was no benefit for DM skin disease⁷⁸.

A large multicenter randomized controlled trial has now been completed in which 48 patients with JDM, 76 with adult DM, and 76 with adult PM were randomized to receive rituximab (575 mg/m² or 750 mg/m² per dose for two weekly infusions or placebo at weeks 0 and 1 followed by placebo, or placebo followed by rituximab at weeks 8 and 9), utilizing a randomized placebo-phase design⁷⁹. Although 83% of these treatment-refractory patients responded to rituximab and could significantly decrease corticosteroid dose after rituximab therapy, there was no difference in the time to response in the two treatment arms, the primary trial endpoint. However the study was not designed to have adequate power to detect a significant difference between treatment arms within the JDM cohort.⁷⁹ For JDM, the time to response was a median of 12 weeks, compared to 20 weeks overall. It is unclear from this trial whether rituximab is effective in myositis or whether there was a failure of trial design, including too short a placebo period to detect a difference in the clinical response of the early-rituximab group vs. placebo, and/or a failure of the preliminarily validated outcome measures⁸⁰. Patients with JDM, with anti-synthetase or anti-Mi2 autoantibodies, and those with a lower disease damage score appear to have a more rapid response to rituximab⁵³. Safety concerns with rituximab include infusion reactions (many of which respond to adequate premedication regimens), infections, and, rarely, progressive multifocal leukoencephalopathy^{79;81}. Accordingly, we do not recommend routine readministration of rituximab at scheduled times after completion of one course of rituximab, but rather when there is evidence of worsening disease activity following B cell return. Whether rituximab will prove useful in the treatment of early disease or whether other B cell-depleting agents may be helpful in the IIM remains to be determined.

The biologic rationales for the use of anti-tumor necrosis factor (TNF) in the therapy of JDM are that elevated levels of TNF are present in the muscle and peripheral blood of patients with active disease^{57;60} and that a pro-inflammatory TNF promoter polymorphism is associated with the development of calcinosis and ulcerations⁸². Reports suggest mixed benefit and some worsening in patients receiving anti-TNF therapies. Perhaps the greatest benefit observed was with use of infliximab in open-label studies of treatment-refractory JDM patients. One case series of 5 refractory JDM patients given infliximab reported improvement in muscle strength and other core set activity measures, as well as in calcinosis⁸³. A larger study of 30 JDM patients treated with infliximab found improvement in muscle strength and physical function, muscle enzyme levels, skin rashes, and physician global disease activity in more than 70% of treatment-refractory patients⁸⁴. Calcinosis improved in 46%. Improvements were not as dramatic or frequent using other anti-TNF agents, including etanercept and adalimumab⁸⁴.

A randomized controlled trial of infliximab in 11 refractory adult PM patients and 1 with DM had mixed success; approximately 25% had improved muscle strength and function during the randomized portion of the trial⁸⁵, and 7 of 12 patients (58%) met criteria for the IMACS preliminary definition of improvement. Other reports of infliximab to treat adult patients with refractory DM and PM also show mild benefit⁸⁶, but several open-label trials later reported disease progression or worsening with infliximab therapy in refractory adult DM and PM patients⁸⁷. In one trial of infliximab in 9 adult patients with refractory DM, PM, or IBM, 3 improved by the IMACS definition of improvement, 4 were unchanged, and

2 worsened; no patient improved in muscle strength by manual muscle testing. Muscle edema on MRI worsened in 5 patients, and pro-inflammatory cytokines and type I interferon activity increased after treatment⁸⁸.

An open-label trial of etanercept in 10 patients with refractory JDM reported mild improvement in overall disease activity by the Disease Activity Score, but no improvement in muscle strength, function, or skin activity⁸⁹. In contrast, in a randomized placebo-controlled trial of etanercept in adult DM, 11 etanercept-treated patients had a longer time to disease flare and greater ability to lower prednisone dose compared to 5 patients receiving placebo⁹⁰. Although core set measures of disease activity, including physician global activity, muscle strength, and physical function, improved during the 52-week trial, there was no difference between etanercept-treated patients and those in the placebo group. Reports of the development or exacerbation of adult DM after use of etanercept or adalimumab for treatment of arthritis suggest further caution in the use of anti-TNF therapies in the treatment of JDM⁹¹.

The evidence for using other biologic therapies to treat JDM is even sparser, consisting of single open-label trials in adult IIM patients or case reports in treatment-refractory JDM patients. For example, an open-label trial of anakinra in 15 refractory adult DM, PM, and IBM patients showed clinical response in 7 patients, which correlated best with those who had higher extramuscular activity, muscle macrophages, and IL-1 expression⁹². There are no reports to date of IL-1 blockade in JDM. In an early phase IB randomized, placebo controlled, dose-ranging study of the anti-interferon γ monoclonal antibody sifalimumab in adult DM and PM, the type I interferon gene signature and interferon-inducible proteins were suppressed in the peripheral blood by 53–66% from 28–98 days after administration and in the muscle by 47% at day 98. Patients with a greater degree of improvement in manual muscle testing scores showed greater inhibition of the interferon gene signature⁹³.

A single patient with severe refractory JDM gained improvement in muscle strength, function, and skin activity, including cutaneous ulcerations, after administration of abatacept⁹⁴. A beneficial effect of tocilizumab was reported in two adult patients with refractory PM who had improved CK levels and muscle edema on MRI⁹⁵.

Alemtuzumab (CAMPATH 1H) at an immunoablative dose was used to treat a single patient with severe refractory JPM⁹⁶. Clinical improvement began 6 months after the infusion and continued to 12 months; two courses were required for sustained remission, with achievement of normal strength and function, normal enzyme levels, and ability to taper off all immunosuppressive medication. A nonablative regimen of alemtuzumab was examined in an open-label trial of 13 patients with IBM in which strength improved by a mean of 11% after 6 months of therapy, and 8 patients (62%) had moderate improvement in their daily life functional activities, which compared favorably to the prior decline in strength and function before the initiation of treatment. Endomysial inflammation, including expression of CD3+ T lymphocytes and stressor molecules in the muscle, was reduced following therapy⁹⁷.

Cell-based therapy has been reserved for treatment-resistant and life-threatening IIM. Three patients with severe treatment-refractory JDM who failed to respond to a number of conventional therapies, improved dramatically after autologous stem cell transplantation^{98;99}. Two of these JDM patients who were wheelchair bound and had severe, extensive disease activity entered sustained remission after an immunoablative conditioning regimen of fludarabine, cyclophosphamide, and antithymocyte globulin, and engraftment of a CD3/CD19-depleted graft. These subjects had near normalization of strength and function and discontinued other medications; one patient also had dissolution of extensive calcinosis⁹⁹.

Treatment of skin disease and rehabilitation

Evidence of a role for ultraviolet (UV) radiation in the etiology of DM and other systemic autoimmune diseases is mounting. A direct relationship was found between UV radiation exposure, based on UV surface exposure at the patient's residence location, and the proportion of patients with DM versus PM, as well as the proportion of patients with DM-associated MSAs, including anti-p155/140 and anti-Mi-2 autoantibodies^{5;100}. Ultraviolet radiation may lead to local inflammation in the skin and alter the expression of autoantigens^{101;102}. Daily application of sunscreens protecting against both UVA and UVB light with an SPF of at least 30 and reapplication after 2 hours in the sun is recommended for patients with JDM, based on expert consensus^{103;104}. Use of other photoprotective measures, such as sun avoidance, photoprotective clothing, wide-brimmed hats, and use of laminated glass in car windows may also be helpful¹⁰⁵.

Many therapeutic agents used to treat muscle disease are also effective for treating cutaneous disease. Specific use of topical corticosteroids or topical immunomodulators (tacrolimus, pimecrolimus) can be helpful for limited rashes when disease activity is confined to the skin and not amenable to systemic therapy, or for more severe rashes, including scalp involvement¹⁰³. Antihistamines and moisturizers are helpful for treating associated pruritis, given the presence of dermal mast cells in the skin of JDM patients¹⁰⁶. Hydroxychloroquine, which inhibits Toll-like receptor activation, has anecdotally been helpful as an adjunctive agent and has been shown to improve cutaneous and renal disease activity and prevent disease damage in lupus¹⁰⁷. Cutaneous ulcerations have anecdotally been reported to improve with IVIG, cyclophosphamide, abatacept, as well as with the surgical use of artificial skin and wound debridement protocols^{94;108}.

Therapeutic approaches for the treatment of calcinosis, which are based on small open-label case series and reports, include aggressive anti-inflammatory therapy for the underlying JDM disease activity, such as treatment with IVIG, IVMP pulses, mycophenolate mofetil, cyclophosphamide, infliximab, abatacept, and others, with reports of improvement in calcinosis lesions in more than half of patients^{69;83}. Medications that alter metabolism of calcium or phosphorous, such as calcium channel blockers, aluminum hydroxide, and probenecid, have had mixed success^{109;110}. In 8 patients with JDM, bisphosphonates, particularly pamidronate, which inhibit the conversion of calcium phosphate into crystalline hydroxyapatite and the nucleation of hydroxyapatite, as well as inhibit macrophage function, were reported to improve calcinosis lesions and arrest progression^{109;110}. Sodium thiosulfate, a calcium chelator and vasodilator that has been used to treat calciphylaxis, was reported to improve severe calcinosis in a few patients when applied topically and administered intravenously⁹⁴. Surgical resection, extracorporeal shock wave lithotripsy, and carbon dioxide laser therapy may improve associated pain and functional disability for severe lesions^{109;110}.

Aerobic fitness is a significant health challenge to JIIM patients. Studies have documented decreased aerobic capacity related to disease activity, muscle damage, and duration of active disease¹¹¹. However, evidence is slowly accruing that exercise training for patients with JIIM is safe and beneficial. A single isometric strengthening exercise session did not increase muscle inflammation in children with active or inactive JDM, as assessed by serum muscle enzymes and MRI¹¹². However, longer term interventions are needed. Several studies in adult IIM have found that isometric and isotonic strengthening, range of motion, and aerobic exercise of 6–24 weeks duration were safe in patients with inactive or chronic active disease, without inducing muscle inflammation. Most of these 16 primarily uncontrolled studies also documented improvement in strength, muscle endurance, physical function, and quality of life¹¹³. A single open-label pilot trial in 10 JDM patients with mild, chronic disease examined the effects of supervised, twice-weekly aerobic and resistance

exercise training¹¹⁴. Deleterious effects on muscle enzymes were not observed. On the other hand, muscle strength and function, aerobic conditioning, bone mass, muscle mass, global disease activity, and health-related quality of life all improved after 12 weeks of exercise training.

Conclusion

The JIIM are heterogeneous diseases defined by clinicopathologic groups and myositis autoantibody phenotypes, which segregate patients sharing similar demographic and clinical features, laboratory abnormalities, and prognoses into more homogeneous subsets. These phenotypes are similar in children and adults within the same subgroup. Treatments have advanced to include more aggressive approaches in the initial treatment of JDM, typically consisting of daily oral prednisone and methotrexate, often in conjunction with another medication. Thus far, several open-label studies and a few randomized trials support the use of several drugs and biologic agents for patients with treatment-refractory disease, severe illness manifestations, and poor prognoses. Attention to the therapy of skin disease, including photoprotective measures, and rehabilitation are also important. Recognition of the heterogeneity of juvenile myositis will lead to tailored, individualized therapies aimed at optimizing each patient's outcome. In addition, the use of validated core set outcome measures has laid a foundation for needed randomized trials and quality clinical studies that should better inform future therapies.

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Key Points

- Juvenile dermatomyositis is the most common clinicopathologic form of the juvenile idiopathic inflammatory myopathies (JIM), but juvenile polymyositis and overlap myositis are additional distinct groups with higher morbidity and mortality rates.
- Myositis-specific and myositis-associated autoantibodies define several distinct serologic subgroups of juvenile myositis, which share many features with those of adult JIM patients with the same autoantibodies. Of these, anti-p155/140 and anti-MJ autoantibodies are the most common in juvenile JIM.
- Based on expert consensus and a randomized controlled trial, the combination of daily prednisone with methotrexate is the initial treatment of choice for juvenile dermatomyositis, and other agents, including intravenous methylprednisolone, intravenous immunoglobulin, and cyclosporine may be used in combination with them or serve as alternative agents to methotrexate.
- Early evidence primarily from open-label studies and one randomized controlled trial suggest a role for additional drug and biologic therapies in treatment-refractory patients.

Synopsis

The purpose of this review is to inform the reader about recent trends in the classification of the juvenile idiopathic inflammatory myopathies and the emerging standard of treatment for the most common form of JIIM, juvenile dermatomyositis.

Table 1
A clinicopathologic classification of the juvenile idiopathic inflammatory myopathies (JIIM)

CLINICOPATHOLOGIC PHENOTYPE	FREQUENCY IN JIIM	ASSOCIATIONS & COMMENTS	REFERENCES
Dermatomyositis (DM)	85%	Most common form of JIIM in children with median age at onset of 7.5 years and female predominance. Characterized by Gottron's papules or heliotrope rash, and CD4+ T cells and dendritic cells in perivascular distribution in muscle with a type I interferon signature. Approximately 50–60% of patients have a chronic course, and 24–40% have a monocyclic course of illness. Up to 25% have skin or gastrointestinal ulcerations. Calcinosis is seen in 25–40% and lipodystrophy in ~10%, with a spectrum of other associated manifestations.	5;8;10;11;15;18
Overlap myositis	6–12%	Patients meet criteria for another autoimmune disease, most frequently systemic sclerosis, systemic lupus erythematosus, juvenile idiopathic arthritis, localized scleroderma, Sjögren's syndrome, or type I diabetes. Raynaud's phenomenon, interstitial lung disease, arthritis, sclerodactyly, and calcinosis are more frequent in this subgroup, and mortality is high, often related to lung disease.	5;10;19;20
Polymyositis (PM)	4–8%	Defined by the absence of the characteristic DM rashes. Pathogenesis involves CD8+ endomysial infiltration in muscle. Patients tend to be older (pre-teen or teenage), have higher CK level, and more severe illness onset, with frequent falling episodes as a sign of distal weakness, myalgias, more frequent cardiac involvement, and intermediate mortality.	5;10;22
Anyopathic or hypomyopathic DM	1%	DM skin rashes, either without muscle weakness or with subclinical muscle weakness detected only by additional testing (e.g., elevated serum muscle enzymes or abnormal EMG, muscle biopsy, or MRI). Approximately 25% of patients develop JDM within 3 years. Calcinosis has been reported in only 4%, and cutaneous ulcerations and interstitial lung disease are very rare. None of the children have malignancy, in contrast to adults with clinically amyopathic DM where these associated features are common.	24;25;28
Inclusion body myositis (IBM)	Rare	Characterized by slowly progressive proximal and distal weakness, low serum CK, and rimmed vacuoles on trichrome stain of muscle biopsy, with poor responses to immunosuppressive therapy. Only a few case reports in teenage boys, whereas IBM is a major clinical subgroup in adults, suggesting a degenerative pathogenesis and/or environmental triggers that are present only in older adults or that have long latency.	3;115
Cancer-associated myositis	< 1%	Malignancy in association with JIIM is so uncommon that routine screening for cancer is generally not warranted, in contrast to adults with DM and PM, where a malignancy screen is routinely performed, due to a paraneoplastic association within 2 years of myositis onset. Atypical illness features, such as prominent adenopathy, hepatosplenomegaly, palpable masses, and atypical rashes, have been proposed as part of a profile of indicators that may be indicative of an underlying associated malignancy that have been observed in most of the 17 reported cases of cancer associated with JIIM. The most common cancers in children include lymphoma, leukemia, and solid organ tumors.	3;10;29–31
Focal myositis	1–2%	Characterized by a subacute, often painful intramuscular swelling or mass in a single muscle group, sometimes preceded by trauma, with histologic features of myositis. The most common sites of involvement are the thigh muscles, gastrocnemius, brachialis, and sternocleidomastoid. These lesions often spontaneously resolve, but immunosuppressive therapy or surgical resection may be beneficial in refractory cases.	8;32;33
Orbital myositis	1–2%	A focal myositis of the rectus muscles, which presents with ocular pain, headache, diplopia, proptosis, ocular injection, limited ocular mobility, and periorbital edema. Children may have atypical presentations, including emesis, anorexia, lethargy, abdominal pain, and weight loss. Importantly, inflammation of an orbital muscle must be distinguished clinically from thyroid-associated orbitopathy, but the differential diagnosis also includes rhabdomyosarcoma, lymphoproliferative disease, IgG4-related disease, or histiocytosis X. Pediatric cases also differ from their adult counterparts in that they are more likely to be bilateral on presentation or associated with uveitis, disc edema, or eosinophilia. Orbital	8;116–119

CLINICOPATHOLOGIC PHENOTYPE	FREQUENCY IN JIIM	ASSOCIATIONS & COMMENTS	REFERENCES
Immune-mediated necrotizing myopathy	1%	myositis may be seen following an infection, such as Group A streptococcus, or in the setting of other autoimmune conditions, including inflammatory bowel disease, linear scleroderma, or Kawasaki disease.	6;46
Macrophagic myofasciitis	<1%	PM or DM in which the muscle biopsy demonstrates prominent muscle necrosis and little inflammation. Thought to be mediated by autoantibodies, including anti-signal recognition particle (SRP) or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) reductase.	34–36;38
Eosinophilic myositis	<1%	An inflammatory myopathy thought to be related to aluminum-adjutant vaccines. Presents with prominent macrophagic infiltrates and aluminum detectable in the muscle. Symptoms include myalgias, arthralgias, muscle weakness, chronic fatigue, and fever. In children, additional features include hypotonia, motor delay with an inability to stand or walk, and failure to thrive. Typically, vaccination predates the diagnosis by 2–12 months, and childhood-onset cases are generally in the first 5 years.	120–123
Granulomatous myositis	<1%	Prominent eosinophilic infiltrates on muscle biopsy, often accompanied by peripheral eosinophilia. May be idiopathic and true polymyositis or focal in nature. May also be drug induced, related to a parasitic infection, or to an underlying hyper eosinophilic syndrome. In children, it is particularly important to exclude muscular dystrophies, including calpainopathy, Becker's dystrophy, and gamma sarcoglycanopathy (LGMD2C), which have been reported to present with eosinophilic myositis.	124;125
Proliferative myositis	Rare	Granulomas prominent in the muscle, which may be idiopathic or seen in association with Wegener's vasculitis, sarcoidosis, or tuberculosis.	126;127
Graft-versus-host myositis	Rare	A very rare benign pseudosarcomatous lesion of skeletal muscle. May be diagnosed with fine-needle aspiration cytology, which shows hypercellular and polymorphic lesional cells and distinctive ganglion cell-like cells. The majority of lesions resolve spontaneously within 4 months, and surgical resection is used for the remaining lesions.	128

Abbreviations: JIIM, juvenile idiopathic inflammatory myopathies; DM, dermatomyositis; PM, polymyositis; CK, creatine kinase; EMG, electromyogram; MRI, magnetic resonance imaging; IBM, inclusion body myositis.

Table 2
A serologic classification of the juvenile idiopathic inflammatory myopathies (JIIM)

SEROLOGIC GROUP	FREQUENCY	CLINICAL SUBGROUP ASSOCIATION in JIIM	COMMENTS	REFERENCES
MYOSITIS-SPECIFIC AUTOANTIBODIES (MSA)				
Anti-p155/140 (TIF1-)	23–30%	JDM and JDM with overlap myositis	Associated with extensive photosensitive skin rashes, including the characteristic rashes of JDM, malar rash, V- and shawl-sign rashes, and linear extensor erythema, as well as peritongual capillary changes, skin ulceration, and generalized lipodystrophy. Patients frequently have a chronic illness course. Not associated with cancer-associated myositis, which differs from adult IIM patients with this autoantibody.	5;18;39;41;43
Anti-MI (NXP-2)	20–25%	Primarily JDM	Frequent muscle cramps, dysphonia, joint contractures, and a monocyclic illness course. This autoantibody group appears to have more severe illness, with some reports of increased calcinosis, frequent muscle atrophy, more frequent hospitalizations and gastrointestinal ulceration.	5;39;44;45
Anti-aminoacyl tRNA synthetases (Jo1 synthetase & non-Jo1 synthetases)	2–4%	JDM, JPM, & overlap myositis	More common in JPM (9%) and juvenile overlap myositis patients (8–13%). Frequent interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, fevers, and mechanic's hands, similar to adults with these autoantibodies. Among the MSA phenotypes, this group has the highest mortality, due to ILD.	5;19;20;39
Anti-SRP	1%	JPM	More common in JPM (18%). Seen primarily in African-American girls with JPM who have severe to profound proximal and distal muscle weakness, frequent falling episodes, Raynaud's phenomenon, very high CK levels, wheelchair use, and a chronic illness course. Cardiac disease is also likely associated, and these patients are refractory to a number of therapies, similar to adult IIM patients with anti-SRP autoantibodies.	5;39;46
Anti-Mi-2 (NuRD)	2–13%	JDM & overlap myositis	JDM with classic cutaneous findings of Gottron's papules, heliotrope rash, and malar rash. Predominantly seen in Hispanic patients. Mild disease, but children have higher CK levels than adults with this autoantibody.	5;21;39;45
Anti-CADM-140 (MDA 5)	Unknown	JDM	Associated with DM and clinically amyopathic DM in adults who frequently have rapidly progressive ILD, cutaneous ulceration, and palmar papules, with a high fatality rate. Seven patients with JDM or amyopathic JDM and ILD have been reported with this autoantibody. One JDM patient reported with fatal disease, with rapidly progressive ILD and cardiac disease. To date, most reports from Japan, and mortality has been high.	47;48;129;130
Anti-SAE	0.2%	JDM	Associated with DM cutaneous manifestations, which predate development of muscle symptoms, an absence of constitutional manifestations, and low frequency of ILD.	5;49;131;132
MYOSITIS-ASSOCIATED AUTOANTIBODIES (MAA)				
Anti-UIRNP	5–10%	JDM, JPM, & overlap myositis	More common in JPM (12%) and overlap myositis (20–27%). Associated with arthritis, Raynaud's phenomenon, and sclerodactyly.	5;19;45;133;134
Anti-Ro	2–6%	JDM, JPM, & overlap myositis	More common in overlap myositis (8–15%). Little known about the associated clinical features. Associated with impaired lung function in 1 report. In adults, patients respond well to prednisone alone. May be seen in association with anti-Jo1 autoantibodies.	5;19;134;135
Anti-PM-Scl	1–4%	JDM, JPM, & overlap myositis	More common in JPM (6%) and overlap myositis (10–25%). Based on adult cohorts, this autoantibody is associated with Raynaud's phenomenon, arthritis, ILD, and esophageal	5;19;136;137

SEROLOGIC GROUP	FREQUENCY	CLINICAL SUBGROUP ASSOCIATION in JIIM	COMMENTS	REFERENCES
			dysmotility. Most frequent in Caucasian patients with an HLA DRB1*0301 immunogenetic association.	
Anti-Ku	0.2%	JDM, JPM, & overlap myositis	More common in overlap myositis (2%). Based on adult cohorts, frequently associated manifestations include arthralgia, Raynaud's phenomenon, myalgias, dysphagia, and less commonly, ILD. Patients respond well to corticosteroids alone, except those with lung disease.	21;138
Other MAAs: anti-U2-, U3- or U5-RNP; anti-La; anti-Sm; anti-Th	< 1%	JDM, JPM, & overlap myositis	Each autoantibody is present more frequently in overlap myositis (1–10%). Little known, primarily associated with overlap myositis.	5;19
Myositis autoantibody negative	28– 57%	JDM, JPM, & overlap myositis	Relatively mild disease in this subgroup. This group is likely heterogeneous, with a number of different unrecognized autoantibody groups contained within.	5;19

Abbreviations: JIIM, juvenile idiopathic inflammatory myopathy; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; ILD, interstitial lung disease; CK, creatine kinase; SRP, signal recognition particle; SAE, small ubiquitin-like modifier activating enzyme; DM, dermatomyositis; HLA, human leukocyte antigen.

Table 3

Medications Used to Treat Juvenile Dermatomyositis *

MEDICATION	RECOMMENDED REGIMEN	SUPPORT & COMMENTS	REFERENCES
PRIMARY THERAPY [†]			
Prednisone	Dose starting at 2 mg/kg/day po; maximum 60 mg/day. Gradually tapered by 2–4 week intervals, with a minimum recommended duration of 10–12 months	Daily prednisone is considered the mainstay of treatment for JDM and other JIM, throughout the illness course, and has led to dramatic improvements in mortality (now under 2% for JDM) and functional disability.	3;55;63
Intravenous methylprednisolone (IVMP)	30 mg/kg/day IV; maximum 1 g, 3 days in a row at diagnosis, then optional once weekly	Used as an adjunct therapy with daily corticosteroids during the initial treatment of moderate to severe JDM. Provides better absorption of corticosteroid, aiding in rapid improvement of disease activity. Also valuable for acute or life-threatening manifestations, such as severe dysphagia, interstitial lung disease, myocarditis. May be used later in the illness course for flares or persistent activity.	3;55;59;65
Methotrexate	1 mg/kg or 15 mg/m ² once weekly SQ; maximum 40 mg weekly	Most commonly used adjunct therapy with steroids, used as firstline therapy for moderate to severe disease. Efficacy in combination with steroids is superior to prednisone alone, including a shorter time to inactive disease. Methotrexate used in conjunction with steroids from time of diagnosis results in fewer cataracts, less weight gain, and less reduction in growth velocity, and a lower cumulative dose of prednisone.	54;55;64
Intravenous immunoglobulin (IVIG)	2 g/kg IV; maximum 70 g, every 2 weeks x3, then monthly	Adjunct therapy for moderate to severe disease; usually combined with steroids and methotrexate. Used both as an agent for initial treatment of moderately severe disease and for refractory cases. Rapid onset of action and lack of immunosuppression are potential benefits. May be helpful in patients with acute, potentially life-threatening manifestations (dysphagia, marked weakness, ulceration), as well for treatment of skin disease and calcinosis.	3;55;67
Cyclosporine	2.5–7.5 mg/kg/day po divided bid (maximum 150 mg bid) to maintain trough blood level 300 ng/mL	Preferred agent in European centers compared to other continents. Used for initial treatment, but more so for refractory patients. Efficacy in combination with steroids is superior to prednisone alone, including a shorter time to inactive disease. However, side effects are greater than with methotrexate.	3;54
THERAPIES FOR REFRACTORY DISEASE [‡]			
Mycophenolate mofetil	20–40 mg/kg/day po divided bid or 800–1350 mg/m ² /day	Used to treat severe or refractory disease, with improvements in muscle strength and skin activity and reduction in corticosteroid dose.	65;69
Tacrolimus	Initial dose of 0.04–0.08 mg/kg/day po divided bid (max 2–3 mg bid), with gradual increase to 0.1–0.25 mg/kg/d divided bid (max 3–6 mg bid) to maintain trough level of 10–15 ng/ml	Used for severe or treatment-refractory disease, particularly with severe weakness, interstitial lung disease, or with anti-synthetase or anti-signal recognition particle autoantibodies.	70;71
Cyclophosphamide	500–1000 mg/m ² /month IV	Used for life-threatening disease activity, severe dysphagia, interstitial lung disease, gastrointestinal or cutaneous ulcerations or other forms of vasculitis, or in patients with severe disease activity that is treatment refractory. Improvements in muscle strength and function, skin, extramuscular activity, and calcinosis reported.	72;73
Rituximab	575 mg/m ² or 750 mg/m ² (maximum 1 g) per dose for two weekly infusions	Used for refractory patients who failed to improve on other DMARDs. Approximately 80% of treatment-refractory patients have improved in a	53;75;76;78;79

MEDICATION	RECOMMENDED REGIMEN	SUPPORT & COMMENTS	REFERENCES
Anti-TNF (infliximab, etanercept)	Infliximab: 3–6 mg/kg IV at weeks 0, 2, 6 and then every 4 weeks	<p>randomized controlled trial and in open-label studies. Onset of improvement lags for about 3 months after infusion. Efficacy more toward muscle rather than skin disease activity. Helpful in patients with myositis autoantibodies.</p> <p>Infliximab has best success for JDM in open-label study and small case series of treatment-refractory patients. Reported improvement in muscle strength and physical function, muscle enzyme levels, skin rashes, and global activity in >70% of treatment-refractory patients; calcinosis improved in 46%. Mixed experience in adult DM/PM, and some reports of disease worsening with anti-TNF therapy, which may be related to induction of the interferon signature.</p>	83;84

Abbreviations: po, by mouth; kg, kilogram; JDM, juvenile dermatomyositis; g, gram; JIIM, juvenile idiopathic inflammatory myopathy; IV, intravenous; SQ, subcutaneous; bid, twice a day; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; DMARD, disease-modifying anti-rheumatic drug; TNF, tumor necrosis factor; PM, polymyositis.

* Experience with additional agents with more limited supporting data, as well as the treatment of cutaneous disease, calcinosis, and rehabilitation, is discussed in the text.

[‡]Per the Childhood Arthritis and Rheumatology Research Alliance treatment consensus for moderately severe disease, dietary modifications and dietary consultation if possible (to minimize prednisone weight gain), photoprotective measures, and folic acid are adjunctive primary therapies. Calcium and vitamin D supplementation and referral to physical therapy and/or occupational therapy are also recommended ⁵⁵.

[‡]Combinations of several primary therapies and therapies for refractory disease may also be used.