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REVIEW ARTICLE

Juvenile dermatomyositis: advances in clinical presentation, myositis-specific antibodies and treatment

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Abstract

Background Juvenile dermatomyositis (JDM) is a chronic autoimmune disease characteristic by inflammation of small vessels within the skin, muscle and vital organs. But the clinical features and treatment of JDM have not been fully clarified.

Data sources Databases underwent through PubMed for articles about the clinical features, myositis-specific antibodies of JDM and its treatment, and we selected publications written in English which were relevant to the topic of this review.

Results Clinical features and myositis-specific antibodies may predict the severity and prognosis of disease. Although the mortality rate has been lower with traditional treatments, such as corticosteroid, intravenous immunoglobulin, and disease-modifying anti-rheumatic drugs such as methotrexate, their usages are variable. Novel biological therapies seem to be effective for refractory JDM patients, but more clinical trials are necessary.

Conclusions JDM is a sever disease of childhood. We need to better understand recent advances of JDM in the context of clinical features including skin manifestations, muscle weakness and organ damage, myositis-specific antibodies and their associated outcomes and the treatment of disease.

Keywords Biologic agents · Extramuscular manifestations · Juvenile dermatomyositis · Myositis autoantibodies

Introduction

Juvenile dermatomyositis (JDM) is a chronic childhood-onset autoimmune disease. Its hallmark is inflammation of small vessels and tissue within the skin, muscle and major organs, leading to characteristic rashes of the face and extensor joint surfaces (heliotrope rash and Gottron's papules, respectively), symmetrical proximal muscle weakness, raised serum muscle enzymes in concert with vital organs involvement (such as the lung, gastrointestinal system, heart and joints). This disease is rare but is the most common clinical phenotype of all the juvenile idiopathic inflammatory myopathies (JIIM). In this review, we will concentrate on JDM, as well as the latest advances in understanding of clinical features, myositis-related autoantibodies, interferon relationship with JDM and traditional and novel therapy strategies.

Epidemiology

JDM represents up to 81.2–85% of all patients with JIIMs, which with the incidence of 1.9–4 per million per year and prevalence of approximately 2.5 per million per year [1–3]. Although the median age at onset and at diagnosis is 5.7–6.9 years and 7.4–7.7 years, respectively [2, 4–6], about a quarter of patients are younger than 4 years at disease onset. The ratio of girls to boys is 2.3–1 [7, 8]. It is thought that young age of onset, older age at diagnosis or delays in diagnosis may be associated with a poorer prognosis [7, 9]. About 24.5–37% of patients experience a monocyclic course, 3–25.2% a poly-phasic course, and 50.3–60% of patients have a chronic disease activity [2, 10]. Fortunately, the mortality rates have dropped from over 30% to approximate 2–3% since the introduction of corticosteroids [11]. The differences in incidence between racial groups have not been adequately studied. A study shows the distribution of

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race of JDM for white, African American, American Indian/Alaskan, Asian, and Native Hawaiian has no discernible ethnic/racial propensity [6].

Clinical presentation

Diagnostic criteria

The diagnostic criteria of JDM were described by Bohan and Peter in 1975 [12, 13]. The definite criteria for JDM requires the presence of typical rash (including a generalized photosensitive erythema, a periorbital heliotrope rash or Gottron's papules) as well as at least three of the four features indicating muscle involvement—symmetrical proximal muscle weakness, elevated serum-derived muscle enzyme, characteristic muscle biopsy changes and/or electromyography abnormalities. Whereas a patient with typical rashes and two other criteria of muscle inflammation is considered as probable JDM. More recently, European League Against Rheumatism/American College of Rheumatology sets up a new classification criterion for JIIM that displayed higher sensitivity (93%) and specificity (88%) with biopsies, assigning weighted score for each item [14]. However, this new criterion is not widely used, and it is unsure whether it will be successfully applied for clinical.

Skin manifestations

Heliotrope rashes and Gottron's papules (Fig. 1) are usual features of JDM which strongly suggest the diagnosis [12]. Although rashes can appear before muscle signs, they may be subtle and can often be mistaken or easily missed, such as the psoriasis-form rash felt to be psoriasis as the initial diagnosis. Other skin manifestations and mucous membrane lesions may also occur in JDM, including the shawl sign involving the skin of the upper chest (Fig. 2a, b), facial rash (Fig. 2c), photosensitive erythema, truncal erythema, and oral ulcers, which sometimes can be difficult to distinguish with systemic lupus erythematosus. These rashes can display both acute and chronic inflammation. Scaly rashes can appear anywhere particularly on the extremities [2, 11, 15].

Dystrophic calcification occurs in 17–44% of patients, which manifests as calcium deposition in the skin or subcutaneous, extends to muscle, along fascial planes and widespread calcium exoskeleton [16, 17]. It is pleomorphic and often present at pressure points, such as elbows, digits, knees, and buttocks [18]. As our understanding of calcinosis evolves, it is deemed a marker of higher morbidity and mortality. Although the calcinosis is usually a later complication mostly occurs in 1–3 years after disease onset, it can be present at diagnosis or 20 years later after illness onset [4, 19, 20]. Risk factors for calcinosis are largely limited to retrospective clinical trials, may include diagnosis delays, prolonged period untreated, presence of various disease-related autoantibodies, high disease activity, younger age of illness onset, cardiac involvement and the use of non-steroidal immunosuppressive therapies. Calcinosis can result in skin ulceration, nerve entrapment and joint contractures which can contribute to long-term disability [17, 19, 21, 22]. Likewise, the presence of calcinosis can correlate with higher childhood myositis assessment score (CMAS) levels. These might indicate that the calcinosis occurred in a late period of disease and can persist in disease remission [8].

Another severe rash complication of JDM is skin ulceration (Fig. 2d), which may predict a severe course of disease. They affect up to 20% of JDM. Ulceration is pathologically the result of vasculopathy in the skin, caused by hypoxia and ischaemia of the endartheropathy of the small vessels and may be a vasculopathy signal of other systems. The presence

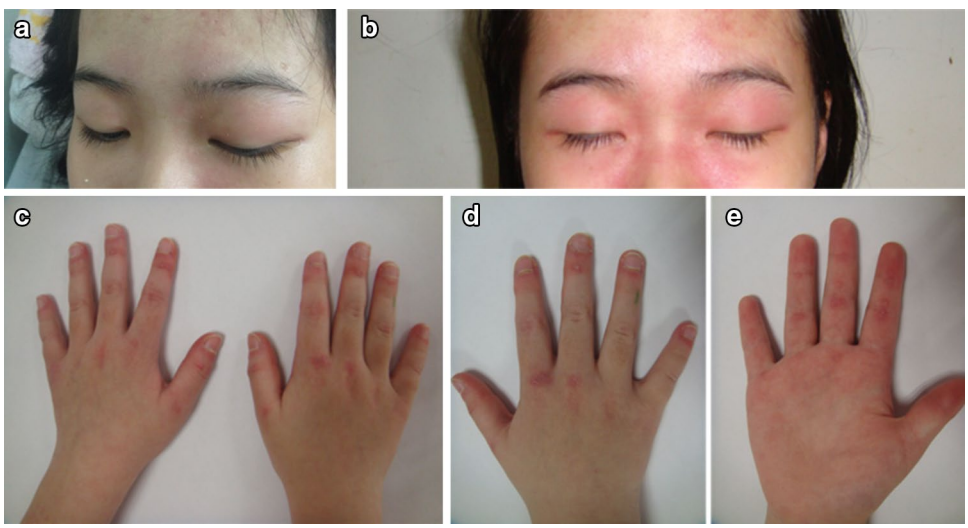

Fig. 1 Pathognomonic rashes seen in juvenile dermatomyositis. **a**, **b** Heliotrope rash—erythema discoloration of upper eyelids; **c**, **d**, **e** Gottron's papules distributed over metacarpal and proximal and distal interphalangeal joints (informed consents for publication were obtained from the patients)

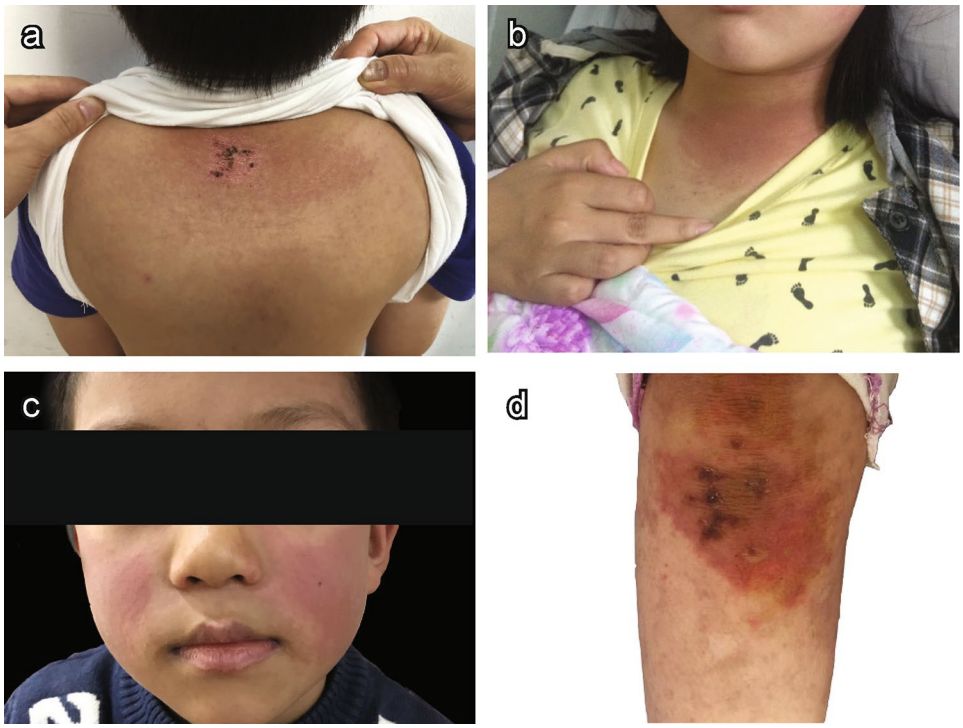

Fig. 2 **a**, **b** The shawl sign (V-sign) rash involves the skin of the anterior upper chest and neck; **c** facial rash—erythema discoloration of cheek, sometimes difficult to distinguish with systemic lupus erythematosus; **d** skin ulceration—knee with several ulcers lesions caused by juvenile dermatomyositis with superficial skin redness (informed consents for publication were obtained from the patients)

of skin ulceration can be associated with ulceration of the intestines, which may lead to haemorrhage, pneumatosis intestinalis or perforation, but the morbidity is uncommon [2, 23, 24]. Vasculopathy sometimes causes oedema or anasarca, which is often associated with cutaneous ulceration. In an UK cohort, Oedema was seen in up to 30% of JDM patients, but anasarca is a rare. Oedema may sometimes be mistaken as nephrotic syndrome and can be seen as a potentially life-threatening manifestation or more severe disease course at diagnosis during exacerbation of the disease [25, 26].

Periungual (nailfold) capillary abnormalities seen in JDM include dilatation, occlusion, haemorrhages, end row capillary loops, increased tortuosity and areas of capillary dropout, which are present in 68–91% at the time of diagnosis [27–29]. They are helpful for differentiating JDM patients from muscular dystrophies and other myopathies. In JDM, nailfold changes represent the evidence of small-vessel inflammation and may associate with both skin and muscle disease activity [10, 30]. Nailfold changes were also correlated with lower CMAS values, higher creatine kinase values, implying that cutaneous and muscular disease were correlated [8]. Low nailfold capillary density was associated with subclinical lung involvement [31], which also supports the opinion that progressive skin disease reflects ongoing systemic disease activity [8]. Nailfold capillaroscopy is used for quantitation of the nailfold end row loops number in JDM, is a commonly and easily non-invasive tool to indicate the disease activity and follow-up disease changes in the clinical practice [27, 32].

Lipodystrophy, occurs in 8–14% of JDM, clinically results in a progressive loss of subcutaneous and visceral fat in general, partial, or local, and might be associated with metabolic sequelae syndrome, such as insulin resistance with acanthosis nigricans, dyslipidaemia and diabetes [33–35]. Patients with lipodystrophy may have an increased risk of disease activity because they have been associated with calcinosis, muscle atrophy and joint contractures [34].

Muscle weakness

Involvement of inflammation in muscle of JDM patients may be severe, demanding early evaluation and intervention, typically results in weakness, loss of endurance, and alterations in physical function. Older children may be better to quantify and complain of early weakness, however, younger patients may present as to be carried more often or difficulties in getting down or up off the floors, dressing, combing hair, climbing stairs and moreover, choking with drinking liquids or voice changes. Muscle weakness is the primary feature of the JDM, usually progressive, symmetric, non-selective and greatly affects proximal muscles [36]. Current clinical tools have been validated as reliable and useful tests to assess muscle strength at diagnosis and follow-up include the CMAS and Manual Muscle Test and the Childhood Health Assessment Questionnaire [37–39].

Lung involvement

Pulmonary system involvement is associated with a poor prognosis, which can present as dysphonia, dyspnea on exertion, abnormal pulmonary function test (PFT), dyspnea at rest, interstitial lung disease (ILD) and pneumothorax. Fatal pulmonary complications in JDM patients are less common than adult-onset IIM. Adult DM patients were five times more likely to die than JDM patients with lung involvement [2, 40]. ILD has been reported in case series with frequencies ranging from 7 to 19% of patients with JDM. ILD can progress rapidly and may be life threatening especially in patients with clinically amyopathic dermatomyositis (CADM), presence of high serum anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies, elevated Krebs von den Lungen-6 and anti-synthetase antibodies [41, 42]. Long-term monitoring for ILD of chest radiography, high-resolution computed tomography (HRCT) scanning and PFT are necessary. HRCT abnormalities were found in 37% of patients, but mostly subclinical. Other imaging abnormalities include nodules, expiratory trapping, linear atelectasis, irregularity, ground-glass opacities, fibrosis and thickening of bronchial walls [41, 43]. A reduction in pulmonary function has been reported in more than half of JDM cases. PFT can show either restrictive or obstructive defects. Diffusion capacity can decrease at early stage of ILD [43, 44].

Cardiac involvement

Cardiovascular involvement is sometimes serious and may be one of the leading causes of death in JDM and juvenile polymyositis [9]. Serious cardiac involvement has been rare reported in JDM patients. A multinational and multicenter study found that the frequency of cumulative damage to the cardiovascular system was 2.9% for 445 juvenile patients [3, 22]. But in the recent years, cardiac events were significantly increased due to the emergence of more sensitive diagnostic techniques of cardiovascular. Myocarditis, congestive heart failure, conduction defects and coronary artery disease have been reported to develop involvement of the cardiac muscle in myositis patients [45]. Increased rates of hypertension and dyslipidaemia [30], a higher prevalence of subclinical cardiac disease than adult dermatomyositis, especially left ventricular diastolic dysfunction also have been reported in JDM patients [46, 47]. Pericarditis has also been described in 12–15% of JDM patients during the disease course. Systolic and diastolic dysfunction may relate with skin disease activity 1 year after the onset of JDM and can persist at inactive stage. Children with JDM have more prevalent electrocardiograph abnormalities and lower heart rate variability compared to age-matched and sex-matched controls. To the best of our knowledge, there are no studies to date prove the relationship between JDM and coronary artery disease [47, 48].

Gastrointestinal tract involvement

Gastrointestinal tract involvement is a worrisome complication with severe prognosis, occurs in 18–44% of JDM cases [15]. It includes dysphagia, gastrointestinal reflux, bowel dysmotility, delayed gastric emptying and gastroparesis, vasculitis of stomach, ulceration, haemorrhage, perforation and other features of liver, small intestine, colon, and rectum disorders [49]. Oropharynx and upper esophagus are mostly involved in patients with JDM, and oropharyngeal dysphagia is well recognized. Younger patients may present as hoarseness of voice, inability to swallow food bolus, coughing while eating, reflux symptoms and laryngitis. Older or adult patients mainly suffer from difficulty with solid and dry foods, feeling of food stuck in the throat and coughing while eating [49]. For severe patients, nasogastric feeding is advised for short periods to reduce the risk of aspiration. Abdominal pain, constipation, or nausea, can also be an early feature. Vasculitis and occlusive thrombi in gastrointestinal tract vessels play a significant role in pathogenesis, can lead to acute enteropathy in JDM patients. Persistent abdominal pain, ischemic ulcers and perforation can be signs of potentially life-threatening manifestation of JDM that warrants aggressive investigation [23, 50].

Other organ involvement

Arthritis is commonly documented in JDM, and it may present as primary joint disease or secondary to the muscle disease, if extensive, may make assessment of weakness challenging [50–52].

Myositis-specific antibodies

Biomarkers of disease autoantibodies are believed to have a key role in the pathogenic pathways of myositis, and each child typically carries a single antibody. Traditionally, autoantibodies have been divided into two major groups, myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs) (Table 1) and they are present in over 60% of JDM cases [53]. MSAs/MAAs in children have been demonstrated to associate with specific clinical manifestations, identifying specific subsets of inflammatory myopathies, responses to therapy and prognosis [54, 55].

MAAs

MAAs are less specific for myositis. They are commonly present in JDM with other mixed connective tissue diseases (CTDs), which principally with scleroderma [56]. The

Table 1 MSAs and MAAs in juvenile dermatomyositis

Autoantibodies	Target autoantigen	Frequency (%JDM)	Clinical complications
Myositis-associated autoantibodies (MAAs)			
Anti-PM-Scl	Exosome-associated PM-Scl-75	3–5	ILD, cardiac involvement, arthritis, mechanics hands, Raynaud's phenomenon and CK level; overlap syndromes
Anti-U1-snRNP	U1-snRNPs	3–8	Considered good prognosis in myositis; overlap syndromes
Anti-Ku	70-and 80-kDa Ku hetero-dimers	< 1	ILD, Raynaud's disease, arthralgia, and reflux
Anti-Ro52	Ro52	6	Commonly occur in myositis patients; associated with other MSAs (especially anti-Jo-1 and anti-MDA5 autoantibodies); overlap syndromes
Myositis-specific autoantibodies (MSAs)			
Anti-p155/140	TIF-1γ	22–29	Severe cutaneous disease (lipodystrophy, skin ulceration and edema)
Anti-MJ	NXP2	18	Predicts poor prognosis; frequent muscle cramps, atrophy, joint contractures, and dysphonia; gastrointestinal ulcerations and bleeding
Anti-MDA-5 (CADM-140)	MDA5	7–33	Rapidly progressive ILD; higher IL-18, IL-6, and ferritin; fever and milder muscle disease (low CK levels)
Anti-Mi-2	NuRD complex	4–10	Cutaneous features; better prognosis (milder muscle, decreased risk of ILD, malignancy, responds well to standard therapies)
Anti-SAE	SAE	< 1	Initially amyopathic disease in adult DM
Anti-ARS (anti-Jo-1 anti-OJ, anti-EJ, anti-KS, anti-PL-7, anti-Zo, anti-Ha, anti-PL-12)	ARS	6–12 1–3	Antisynthetase syndrome: fever, ILD, Raynaud's phenomenon, mechanics hands, non-erosive arthritis, mortality rate; better prognosis compared to anti-Jo-1 negative
Immune-mediated necrotizing myopathy			
Anti-SRP	SRP	Extremely rare	Severe symmetric muscle weakness, Raynaud's phenomenon, very high CK levels, cardiac disease, dysphagia, ILD
Anti-HMGCR	HMGCR	< 3 in JM	Necrotizing autoimmune myositis, muscle weakness; worse disease course

JDM juvenile dermatomyositis, *ILD* interstitial lung disease, *CK* creatinine kinase, *CADM* clinically amyopathic dermatomyositis, *DM* dermatomyositis, *JM* juvenile myositis, *U1-snRNPs* small nuclear ribonucleic proteins, *TIF-1γ* transcriptional intermediary factor 1 gamma, *NXP2* nuclear matrix protein 2, *MDA5* melanoma differentiation-associated gene 5, *NuRD* nucleosome remodelling and deacetylase, *SAE* small ubiquitin-like modifier activating enzyme, *ARS* aminoacyl-tRNA synthetases, *SRP* signal recognition particle, *HMGCR* 3-hydroxy-3-methylglutaryl-coenzyme A reductase, *MSAs* myositis-specific autoantibodies, *MAAs* myositis-associated autoantibodies

commonest MAAs in JDM patients include anti-PM-Scl, anti-U1-RNP, anti-Ku, anti-Ro (SSA) and anti-La (SSB) autoantibodies. Anti-PM-Scl autoantibodies are often complicated by an increased risk of ILD, cardiac involvement, high frequency of arthritis, mechanics hands, Raynaud's phenomenon and serum creatine kinase level increased. They are less common in juvenile cohorts (3–5%), have more presenting features shared with scleroderma in patients of JDM, such as severe Raynaud disease [54, 57–59]. Anti-U1-snRNP autoantibodies are more less in JDM/juvenile polymyositis (JPM) (3–8%), usually found in patients with myositis overlap (25–40%), considered a marker of good prognosis in myositis [60, 61]. Anti-Ku autoantibodies are DNA-associated proteins, associated with myositis/scleroderma overlap syndrome, occurring in less than 1% with patients of JDM. It has been reported to have an increased frequency of ILD, Raynaud's disease, arthralgia, and reflux [62]. Autoantibodies to SSA (Ro60, Ro52) and SSB (La) commonly occur in myositis patients. Anti-SSA autoantibodies are present in approximately 6% of JDM patients and

14% of patients with juvenile myositis. Anti-SSB autoantibodies are reported in 2–7% of PM/DM and 4–12% of overlap patients. Researchers found anti-Ro52 autoantibodies may be associated with other MSAs, such as antisynthetases, especially anti-Jo-1 autoantibodies (56–72%) and anti-MDA5 autoantibodies. Moreover, anti-Jo-1 co-occurs with anti-Ro-52 autoantibodies potentially identifying more severe ILD and poorer prognosis than patients with anti-Jo-1 alone [57, 63–65]. But recent researches show the outcome that juvenile myositis with anti-Ro52 autoantibodies alone also present increased ILD, more severe disease and poor prognosis [66, 67].

MSAs

Different MSAs are associated with the presence of specific phenotypes and prognosis in patients with myositis. MSAs are present in more than 50% of juvenile myositis patients [54, 55]. Moreover, a recent study shows MSAs were detected in 95.2% of Japanese patients with JDM [68].

Autoantibodies to a 155-kDa protein and 140-kDa protein (anti-p155/140 autoantibodies) have been identified as transcriptional intermediary factor 1 gamma (TIF-1γ) and TIF-1α. Anti-p155/140 autoantibodies were commonly found in JIIMs/JDM. They occur in 18–35% of JIIM patients, particularly those with JDM (22–29%) or overlap myositis in children, but they have not been reported in patients with juvenile polymyositis or other CTDs [34, 54, 55, 57, 66, 68]. Anti-TIF-1γ autoantibodies have been associated with extensive photoerythema, including Gottron's papules, facial, V-neck rashes, and linear extensor erythema. Moreover, they may associate with more severe cutaneous diseases, such as a lipodystrophy, skin ulceration and edema [34, 69, 70]. In addition, this autoantibody was frequently associated with malignancy in adult DM patients [57]. However, DM/PM patients with anti-TIF-1γ were more likely without ILD or lower incidence of muscle weakness [68, 70].

Another frequent MSA in JDM is anti-MJ autoantibody, which target the nuclear matrix protein 2, was first reported in 18% of JDM, presenting in 12–23% of JIIM patients. This autoantibody was primarily found in those with JDM. Anti-MJ autoantibody predicts poor prognosis. The presence of anti-MJ autoantibody in children significantly associates with frequent muscle cramps, atrophy, joint contractures, and dysphonia, which is occurring in about half of patients. Some studies suggested anti-MJ autoantibody may associate with calcinosis and absence of truncal rashes [71]. Furthermore, patients with anti-MJ tended to have more severe muscle weakness and high incidence of gastrointestinal ulcerations and bleeding, resulting in worse disease outcome and impaired functional status [55, 57, 71, 72].

Anti-MDA-5 autoantibody is directed against the melanoma differentiation-associated gene 5, which known as CADM-140 (originally termed p140 and associated with clinically amyopathic DM). Mostly, anti-MDA5 is not related to PM. Although anti-MDA-5 is a less common MSA, it appears to be more pronounced in Asian JDM cohorts [73]. In Japanese JDM patients, anti-MDA5 antibodies occurred in 23.8–33%, however, these autoantibodies were identified in only 7% of JDM patients from a UK research [68, 73]. Patients with anti-MDA5 antibodies associate with a typically higher rate of developing ILD. But the expression of ILD is different between Asian region and US or European region. Among the Japanese patients, anti-MDA5 autoantibodies were associated with rapidly progressive ILD, which correlated with higher serum levels of interleukin (IL)-18, IL-6, and ferritin than patients without progressive ILD. In the UK JDM registry, patients with anti-MDA5 autoantibodies had not been found with rapidly progressive ILD [42, 73, 74]. In addition, fever and milder muscle disease (low CK levels) are common in patients with anti-MDA-5 autoantibodies, but may complicated by cutaneous ulcers and arthritis which were rare in the Japanese series [74, 75].

Anti-Mi-2 autoantibody is a traditional MSA less frequently identified in JDM, against the nucleosome remodelling and deacetylase complex. This antibody has been demonstrated to be a specific marker for DM, presenting in 4–10% of JDM patients [54, 55]. Anti-Mi-2 autoantibody is significantly correlated with a range of cutaneous features including Gottron's papules, heliotrope rash, V-neck and shawl sign rashes, and cuticular over-growth in adult DM patients, however, unlike in adults, these cutaneous features have no significance in children with anti-Mi-2 [76, 77]. Anti-Mi-2 autoantibody suggests a better prognosis, such as milder muscle involvement and a decreased risk of ILD and malignancy, and responds well to standard therapies [78, 79]. Another antibody of DM is anti-small ubiquitin-like modifier activating enzyme (SAE) autoantibody. Studies found it is less frequently identified in JDM (< 1%) and a recent study presents that no patient was positive for anti-SAE autoantibodies [68].

Anti-ARS are a group of autoantibodies that target aminoacyl-tRNA synthetases (ARS), including anti-Jo-1, anti-OJ, anti-EJ, anti-KS, anti-PL-7, anti-Zo, anti-Ha and anti-PL-12. They more often occurred in adult myositis patients than patients of juvenile myositis. Among anti-ARS autoantibodies, anti-Jo-1 is most reported, occurring in 9–24% of adult patients with IIM and in 1–3% of JDM patients, respectively [54, 60, 80]. Patients with anti-Jo-1 positive alone may have a better prognosis compared to anti-Jo-1 negative patients, because non-anti-Jo-1 autoantibody presents a higher risk of ILD [60]. Other autoantibodies

of anti-ARS were found less common, totally occurring in approximately 6–12% of patients. Patients with anti-ARS may have similar syndrome, classed as antisynthetase syndrome, which is characterized by fever, ILD, Raynaud's phenomenon, mechanics hands, non-erosive arthritis and the highest mortality rate among MSAs. Juvenile myositis with these autoantibodies also frequently associates with these syndromes [9, 57, 60].

The other group of MAS is immune-mediated necrotizing myopathy (IMNM) autoantibodies, which mainly composed of anti-signal recognition particle (anti-SRP) and the anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies. Both antibodies are considered as fundamental tools to diagnose IMNM [81–83]. Anti-SRP autoantibodies have been detected in 4–13% of patients. They have also been extremely rare described in juvenile patients. Anti-SRP patients specifically have an increase likelihood of severe symmetric muscle weakness, dropped head syndrome, Raynaud's phenomenon, very high CK levels, and a chronic illness course, cardiac disease, dysphagia and ILD [57, 84–87]. Autoantibody to a 200-kDa/100-kD protein complex was identified as anti-HMGCR antibody. Patients with anti-HMGCR antibody are often associated with statin use, and accounting for less than 3% of juvenile myositis patients. Younger or juvenile patients with anti-HMGCR positive may have worse disease course. An increased risk of muscle weakness was hallmark of clinical feature described in patients with anti-HMGCR, but it was found less severe compared to patients with anti-SRP [88-91].

Treatment

Corticosteroids

The mortality rates of JDM have dropped from over 30% to around 2–3% and the outcome of JDM children has been greatly improved since the advent of corticosteroids [11]. Corticosteroids have been considered a first-line and central therapy for patients of JDM. However, the optimal dose/route or duration of corticosteroids appears to be unclear. Pediatric rheumatologists mainly administrate corticosteroid doses based on the severity of disease, however, a study showed that different usage of corticosteroids were chosen in patients of similar severity [92]. Studies suggest two main treatment options for prednisone including an initial dose of corticosteroid at 2 mg/kg/day, or lower doses (0.5–1.5 mg/kg/day) advised by some studies [92–94]. Another area of controversy is the initial route of intravenous versus oral therapy. Intravenous methylprednisolone (IVMP) is hypothesized to be better for active JDM patients because of decreased absorption of oral prednisolone, presumably due to active intestinal vasculopathy [95]. The common treatment high dose is IVMP (30 mg/kg/day, 1 g maximum dose, daily for three or more consecutive days), particularly for moderate and severe cases [44, 93]. Some rheumatologists also recommended the continued weekly use of single doses of IVMP, but this was not unanimous [94]. Consensus on timing and rate of steroid tapering was discussed by several organizations, but there was no unified conclusion other than the recommendations of the CARRA recommendations in moderate to severe disease [96]. Duration of steroid depends on the response of therapy and the preferred duration was found ranging from 4 to 24 months [96]. Corticosteroid taper must be initiated after disease stabilization judged by clinical physician based on core set, such as improved or normal of strength and enzymes, table/improved/absent of rashes, and additional criteria. A consensus was reached for waiting until 4 weeks of treatment of prednisone at 2 mg/kg/day, and then would be reduced by 20% if the patient was stable while another consensus was reached on a weaning interval of every 2 weeks on corticosteroid doses from 2 to 0.5 mg/kg, and then every 4 weeks thereafter [94, 95, 97]. Recently, the Pediatric Rheumatology International Trial Organization evidence-based proposal for glucocorticoids tapering/discontinuation in onset patients of JDM has been published [97]. This study provides evidence that it is possible to reach the steroid dose of 0.2 mg/kg/day within 6 months, therefore, avoiding long corticosteroid exposure and the subsequent side effects, considered safer especially for growth impairment.

Conventional disease-modifying anti-rheumatic drug

Methotrexate (MTX) has become a first-line treatment of JDM. Patients treated with MTX could decrease the cumulative glucocorticoid exposure and have smaller increases in body mass index, higher growth velocities and fewer cataracts [98, 99]. A recent randomized controlled trial proved that patients in the prednisone plus methotrexate or cyclosporine A (CSA) group was more likely to achieve remission than monotherapy with corticosteroids [44, 93]. Since superior adverse reactions occurred with CSA, the authors concluded that initial treatment with a combination of corticosteroid and MTX as first-line treatment over CSA. Due to more side effects, the usage of CSA has likely diminished, but remains an option in JDM patients who have persistent rashes, intolerance or contraindications to MTX [44, 100]. Hydroxychloroquine has been used commonly in JDM, mostly for the treatment of predominantly cutaneous manifestations [101]. Mycophenolate mofetil (MMF) and azathioprine (AZA) are less commonly used in JDM [102]. MMF was found effective and well tolerated in patients of JDM from two studies [103, 104]. There is very limited evidence for the efficacy of AZA. Cyclophosphamide was effective for refractory JDM with significant organ involvement,

including skin ulceration, lung involvement, gastrointestinal vasculopathy, and muscle disease. No short-term adverse events occurred [105, 106].

Intravenous immunoglobulin (IVIG)

The treatment of IVIG in JDM is generally accepted to be efficacious as a second-line treatment option, especially for severe or refractory to steroids and methotrexate, or those with predominant skin disease [44, 96, 100]. The usage of IVIG appears to be variable. Monthly administration of IVIG (1–2 g/kg, maximum 70 g) from the beginning is recommended for JDM patients in most reports [100, 107, 108]. Other reports suggest this dose may be given every 2 weeks for first 3–5 times before moving to every month [94, 108]. The benefits of the IVIG administration in JDM have been reported in some studies [44, 109], such as better disease control and cost saving for steroid-resistant patients, and helpful in patients with difficult skin disease, severe weakness or dysphagia.

Biologic agents

Rituximab (RTX), a B cell-depleting monoclonal antibody, directs against CD20+ B cells. B cells play a critical role in the pathogenesis of myositis, which are elevated in the peripheral blood region of DM muscle, and might also secrete pro-inflammatory cytokines during disease activity [110]. Treatment of RTX was effective in case series or case report in patients with refractory myositis disease [110–114]. Then in a large, randomized, double-blind, placebo-phase controlled clinical trial of adult and pediatric myositis treated with RTX, a significant steroid-sparing effect was provided during this trial, and 83% of refractory adult and juvenile myositis patients met definition of improvement [115]. Furthermore, the presence of an anti-ARS (primarily anti-Jo-1 or anti-Mi-2) or youth (JDM vs DM) was predicted to be more efficacious with rituximab therapy [78]. Other studies found that addition of rituximab to the standard therapy was efficacious for both muscle and refractory skin diseases in adult DM and JDM patients [116].

At present, the role of anti-tumor necrosis factor (TNF) agents in JDM is uncertain. There are case series of refractory JDM patients successful treated with infliximab or adalimumab, and reached improvement in muscle strength and calcinosis [117, 118]. Other reports have found that JDM patients got improvement in muscle strength, muscle enzyme levels, skin rashes, and physician global disease activity with the treatment using infliximab [119–121]. A larger research of 66 JDM patients treated with anti-TNF agents (infliximab or adalimumab) indicated significant improvements in muscle and skin involvement [122]. However, another kind of TNF-inhibitors, etanercept, appeared to be ineffective in JDM. Two studies showed that refractory JDM patients treated with etanercept had no significant improvements in muscle strength, function, or skin activity [123, 124].

Abatacept, a soluble fusion protein comprising the human immunoglobulin G and the second signal mediator cytotoxic T lymphocyte-associated antigen 4 have been reported successful in decreasing the calcific lesions, control muscle and skin inflammation, and have halted the progression of calcinosis and reduced corticosteroid burden in case with recalcitrant JDM [125].

Janus kinase (JAK) inhibitor, an important biologic agent has currently been suggested as a potential new-targeted therapeutic regime in refractory JDM. Researchers increasingly considered the pathogenesis of JDM was highly correlated with interferons (IFN). Many studies have reported the dysregulation of IFN-I in blood and muscle of dermatomyositis patients before, and activation of IFN-I may be related to the disease activity and inflammation [126–133]. A recent study found that muscle expression levels of IFN-I score and IFN-II score were significantly higher in JDM patients and correlated with typical histopathologic features of their muscle biopsy samples and more severe disease activity at biopsy. These features further support a pathogenic role of IFN in JDM [134]. Moreover, the IFN-I pathway activation can induce muscle atrophy, capillary network formation and endothelial and muscle fiber injuries in dermatomyositis patients. They suggest the IFN-I plays a key role in the pathogenesis of the disease [135]. JAK acts downstream of IFN which transduce signals to the nucleus to upregulate IFN-stimulated genes [136, 137]. Inhibitors of the JAK-STAT pathway may be useful in JDM, such as tofacitinib and ruxolitinib. The use of JAK inhibitors have been reported by various cases [138, 139]. An additional study about four refractory dermatomyositis patients treated with ruxolitinib for 3 months after the useless immunosuppressants or immunomodulatory agents, these patients presented significantly improvement of facial skin rash, Cutaneous Dermatomyositis Disease Area and Severity Index scores, muscle weakness and their quality of life score. JAK inhibitors were also suitable for JDM patients with evidence of chronic endothelial injury and inflammatory articular manifestations [135, 137, 140].

Conclusions

JDM is a rare autoimmune disease mainly characterized by muscle and skin involvement, represents the main type of idiopathic inflammatory myopathy of childhood. Although the causes of JDM are still elusive, advances in the fields of new immune and nonimmune pathways, related myositis

autoantibodies and genetics, such as dysregulation of IFN-I, are increasingly helping us understand more about the pathogenesis of disease. Early recognizing of typical and severe clinical features of JDM is important for guiding early diagnose, treatment and predicting prognosis. International and national groups are working on developing standard protocols for assessment and therapeutic strategies of JDM. The future challenge is to use the knowledge of dysregulated immune pathways to develop new biologic therapies for patients with refractory JDM.

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Compliance with ethical standards

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