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Polymyositis and dermatomyositis – challenges in diagnosis and management

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ABSTRACT

Polymyositis (PM) and dermatomyositis (DM) are different disease subtypes of idiopathic inflammatory myopathies (IIMs). The main clinical features of PM and DM include progressive symmetric, predominantly proximal muscle weakness. Laboratory findings include elevated creatine kinase (CK), autoantibodies in serum, and inflammatory infiltrates in muscle biopsy. Dermatomyositis can also involve a characteristic skin rash. Both polymyositis and dermatomyositis can present with extramuscular involvement. The causative factor is agnogenic activation of immune system, leading to immunologic attacks on muscle fibers and endomysial capillaries. The treatment of choice is immunosuppression. PM and DM can be distinguished from other IIMs and myopathies by thorough history, physical examinations and laboratory evaluation and adherence to specific and up-to-date diagnosis criteria and classification standards. Treatment is based on correct diagnosis of these conditions.

1. Introduction

The idiopathic inflammatory myopathies (IIMs), also referred to generally as myositis, are classified into polymyositis (PM), dermatomyositis (DM), sporadic inclusion body myositis (sIBM) and necrotizing autoimmune myopathy (NAM). The classification is based on clinical and histological features [1,2]. The incidence of IIMs are fairly low as reported by different research groups. Both children and adults may suffer from DM while PM mainly affect adults. Manifestations of IIMs include chronic muscle weakness and fatigue, and skin exanthema in DM. The pathophysiology involves agnogenic inflammation-mediated muscular and/or connective tissue damage, along with other organ involvement including the heart, lung, joints and gastrointestinal tract. IIMs are therefore characterized as a systemic autoimmune disorder. The mainstay of therapy is immunosuppression with corticosteroids, steroid-sparing agents and other immunosuppressive drugs [1,3,4]. History, physical examination, and multiple laboratory examinations such as serological tests, neurological tests and most importantly, muscle biopsy, help to discriminate between PM and DM, and also other autoimmune disorders or myopathies. Improved knowledge of the pathogenesis will help to more accurately classify disease and establish better diagnostic criteria, which will define treatment algorithms. Moreover, basic researches and clinical trials are necessary to find and develop potential target and therapies in order to improve the prognosis of patients [1–3,5,6].

2. The etiology of polymyositis and dermatomyositis

2.1. The epidemiology of PM and DM

PM is rare in childhood and presents mainly after the second decade of life. The most common time of presentation is between 45 and 60 years of age. DM affects both children and adults with an overall female/male ratio of about 2:1 [7]. In the last twenty years, epidemiological studies have shown a higher incidence and prevalence than historically reported. This may be due to more thorough diagnosis criteria and improved

Abbreviations: APC, antigen presenting cell; AZA, Azathioprine; CAM, cancer associated myositis; CK, creatine kinase; DM, dermatomyositis; EMG, electromyography; HLA, human leukocyte antigen; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IV, intravenous; JDM, juvenile dermatomyositis; MAA, myositis associated antibody; MAC, membrane attack complex; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; MSA, myositis specific antibody; MTX, methotrexate; MUAP, motor unit action potential; NAM, necrotizing autoimmune myopathy; PM, polymyositis; sIBM, sporadic inclusion body myositis; TNF, tumor necrosis factor; Treg, regulatory T cell; UVR, ultraviolet radiation.

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patient access and services. Data from recent epidemiological studies are shown in Table 1. It should be noted that the reported prevalence and incidence of PM and DM are quite variable depending on differences in study methodology, but female gender and urban living appear to be consistent risk factors.

2.2. Hereditary susceptibility

It is well accepted that autoimmunity results from susceptible genes, environmental factors and a dysregulated/dysfunctional immune system [8]. Evidence from case reports, family studies, studies of animal models, candidate gene case-control studies, and whole genome investigations supports a role for genetic factors in the etiology of autoimmune disease [9]. The earliest known cases of familial IIM were reported in the 1950s [10,11], and there is a scarcity of affected sibling pairs and twins. To date, the major histocompatibility complex (MHC) has been shown to be the strongest genetic association for the IIMs, and candidate gene studies have identified shared genetic susceptibility with other autoimmune diseases [12–15]. In IIM, the strongest association is with the 8.1 ancestral haplotype (8.1 AH, HLA-A1-B8-Cw7- DRB1*0301-DQA1*0501-C4A*Q0), a large common haplotype in Caucasian populations in Northern and Western Europe [16,17]. This allele has also been found in other populations including African-American, Japanese, and Spanish but not in Korean or Mexican-American [18–21]. However, which gene or genes contribute to the pathogenesis is not clear. In addition, the non-HLA genes *UBE2L3, CD28, TRAF6, STAT4* [17], *TNF-α* [22], *IKBL (NFKBIL1)* [23,24], *ACTN3* [25], *BLK* [26,27], *IRF5* [28] and *PLCL1* [29] have also been reported as potential risk factors for IIM. Moreover, differences in candidate genes among clinical subgroups have also been identified. For example, *PTPN22, IL18R1, RGS1, IFN-γ* [30] and *IFIH1* [31] have been reported to be associated with PM, while *GSDMB* has been reported as a risk factor for DM [17]. Studies have also been able to correlate HLA with serology, complications and responses to therapy in IIMs.

2.3. Environmental factors

In recent years, evidence has shown that environmental factors play also play a role in the development of autoimmunity. Environmental factors include infection, gut microbiota, drugs, chemicals, pollutants and physical agents [32,33]. Animal models of myositis have been developed that are induced by viruses, drugs, or parasites, providing additional evidence for the likely role of environmental agents in the pathogenesis of IIMs [34].

An online survey of DM patients from the USA and Canada examined environmental factors in patients with or without disease flares over a period of 6 months and found that sun exposure and nonsteroidal anti-inflammatory drug (NSAIDs) were significant factors. In addition, urinary tract infections, gastroenteritis, elevated blood pressure, use of antidepressants, mood changes and relocation were also risk factors for disease flares [35]. The association between ultraviolet radiation (UVR) and DM has been reported by several groups, who have demonstrated that UVR may modulate the clinical and immunologic expression of DM, including the levels of autoantibodies [36–38]. Infection is thought to be an important contributor to immune system activation, and it has been reported that there is a high frequency of opportunistic infections in PM/DM, which may lead to an increase in mortality [39]. An association of viral infections and IIM has also been reported. Coxsackie B virus is associated with increased muscle tropism and is considered to be a potential trigger for PM/DM [40]. Human immunodeficiency virus (HIV) infection has been reported to foster an environment favorable for the development of DM [41]. Notably, PM and DM are associated with a high risk of malignancy [42] and it has been proposed that hepatocellular carcinoma (HCC) and/or a chronic HBV infection may play a role in the pathogenesis of DM through a paraneoplastic mechanism [43,44]. Studies also suggest a possible interaction between tobacco smoking and autoantibody phenotypes of PM/DM [45].

3. The pathology of polymyositis and dermatomyositis

3.1. Animal models

Animal models are important tools for investigating the mechanisms of autoimmune diseases for a number of reasons that include low numbers of patients, an inability to acquire patient samples, ethical issues of doing particular types of studies on humans, variable phenotypes of the disease, non-compliance with study protocols and cost. Compared to other well-researched autoimmune disease such as rheumatoid arthritis and systemic lupus erythematosus, the development of animal model research in PM/DM has been lagging. Dogs and mice are the only two nonhuman species which have been reported to spontaneously develop myositis [46,47]. SJL/J mice spontaneously develop a chronic IIM resembling human myositis which presents as muscle inflammation, centralized nuclei, and muscle fiber necrosis [48–50]. There is limited similarity to human myositis. On the other hand, myositis may be induced in animals by injection with autologous or heterologous muscle homogenates or C protein, purified muscle antigens, viruses, drugs, and naked DNA constructs [34,47]. There are several other animal models which reveal new insights regarding the pathophysiology of IIM [47], but unfortunately, no single animal model fully reproduces the clinical and pathologic features of human IIM.

Table 1
Epidemiological reported data.

Reference	District	Year	Incidence (per 100000)	Prevalence (per 100000)	Gender
[255]	Olmsted County, Minnesota	1976–2007	DM: 0.96 (0.61–1.32)	21.42 (13.07–29.77)	Female: 76%
[256]	Buenos Aires	1999–2009	PM: 0.75 (0.35–1.16) DM: 0.32 (0.1–0.99)	PM: 7.2 (2.9–14.7) DM: 10.22 (4.9–18.8)	Female: 76%
[257]	Spain	1997–2004	PM: 0.89 (0.37–0.41) DM: 0.49 (0.47–0.52)	/	Female > male, $p < 0.001$
[258]	Japan	2003–2010	PM/DM: 10-13	PM/DM: 100-130	/
[259]	Korea	2004–2015	PM: 0.16–0.3 DM: 0.18–0.4	PM: 1.4–2.1 DM: 1.2–2.7	Female: 72.1%
[260]	Quebec, Canada	2003	/	PM/DM: 21.5 (19.4–23.9)	Female: Adjusted OR 2.52 (1.08–3.99)
[261]	USA (commercially insured and Medicare and Medicaid enrolled populations)	2004–2008	PM: 2.46 (2.33–2.59) and 3.53 (3.13–3.94) DM: 1.52 (1.42–1.63) and 1.70 (1.42–1.97)	IIM: 20.62 to 25.32 and 15.35 to 32.74	Female: 67%
[262]	USA (Managed care plan)	2003–2008	IIM: 5.8–7.9	IIM: 14–17.4	Female: 66.8%
[263]	Taiwan	2003–2007	PM: 0.44 (0.4–0.48) DM:0.71 (0.66–0.76)	/	/

3.2. Immunological mechanisms

The immunological signaling pathways and immunopathogenesis involved in PM and DM have been extensively reviewed [3,5,51–53]. In PM, there is evidence of antigen-directed cytotoxic $CD8^+$ T cells surrounding and attacking MHC-I-antigen expressing muscle fibers [52,54–57]. Up-regulation of costimulatory molecules (BB1 and ICOSL) and their ligands (CD28, CTLA-4, and ICOS), as well as ICAM-1 or LFA-1, stabilizes the synaptic interaction between $CD8^+$ T cells and MHC-I on muscle fibers, which means that these muscle fibers act as antigen-presenting cells (APCs) [5,58–60]. Upon activation, perforin granules are released by auto-aggressive $CD8^+$ T cells and mediate muscle-fiber necrosis [61]. In DM, the main target is the vascular endothelium. Early activation of complement C3 by putative antibodies directed against endothelial cells leads to the formation and deposition of C3b, C3bNEO, C4b fragments and C5b–9 membrane attack complex (MAC) on the endothelial cells. These markers can be detected in the serum and muscle of patients in the early phases of the disease [62,63]. Sequentially, the complement deposits induce swollen endothelial cells, vacuolization, capillary necrosis, perivascular inflammation, ischemia, and destruction of muscle fibers, which results in the remaining capillaries developing dilated lumens to compensate for the ischemia [64,65]. At the same time, complement activation leads to the release of proinflammatory cytokines and chemokines [3]. As a result, both innate and acquired immune cells are recruited to the perimysial and endomysial spaces through higher expression of adhesion molecules on endothelial cells interacting with the integrins on immune cells, leading to aggravated immune attack and antibody production [8].

T cell infiltrates in the muscles of patients with PM/DM are dominated by CD28-null T Cells, which are long-lived, proinflammatory and terminally differentiated T cells lacking CD28 [66]. These T cells are linked to resistance against immunosuppression and poor clinical outcome [67]. $CD8^+$ T cells play a critical role in muscle fiber damage especially in PM. T-cell lines expanded from muscle biopsy material of IIM patients consist predominantly of $CD8^+$ T cells and are cytotoxic to autologous myotubes [68]. Clonal expansion of peripheral blood $CD8^+$ T cells with activation of STAT and pZAP70 signaling [69] is more frequently seen in patients of PM than DM [70,71]. Analysis of T cell receptor (TCR) antigen-binding region sequences suggests that T-cell expansion is driven by a common antigen, possibly an autoantigen [56,72].

In DM, complement activation induces capillary destruction and perivascular inflammation. This process is mediated by $CD4^+$ T cells [73]. STAT, forkhead box transcription factor (FoxP3), and pZAP70 expression in peripheral $CD4^+$ T cells is suppressed in active DM, but except for FoxP3, are improved during periods of remission [56]. Immunohistochemical analysis reveals that $FoxP3^+$ regulatory T (Treg) cells predominately locate in perivascular and perimysial infiltrates of DM muscle. In juvenile DM (JDM), Treg cells from peripheral blood show a lower expression of CTLA-4 and are functionally compromised as well [74].

B cells are detected in muscle biopsy specimens of IIM patients. B cells and plasma cells that infiltrate into the perivasculature of DM patients are also found in all subtypes of IIMs [75,76]. Upregulated BAFF signaling and Toll like receptor (TLR) expression [77–82], decreased Breg subset [83], and notably, multiple autoantibody production, demonstrate a highly activated humoral immune state in DM and PM. Researchers analyzed the molecular characteristics of the antigen (Ag) receptor on B cells from muscle and found that BCR affinity maturation and oligoclonal expansion occurred, suggesting a B cell Ag-specific response in the muscle tissue of patients with DM and PM [84,85]. Accordingly, rituximab, a B cell-depleting agent, has been proven to be helpful in some cases of DM and PM [86].

The innate immune system also plays an important role in the pathogenesis of DM and PM. Overexpression of interferon (IFN) -regulated proteins and cytokines have been found in the skin and muscle of patients with DM and PM, suggesting an upregulated "type I IFN signature" [87–90]. Moreover, plasmacytoid dendritic cells (pDC) are a possible source of upregulated IFN in the muscle of DM patients [91]. Besides dendritic cells (DCs) [92], mast cells [93], neutrophils [94] and macrophages [95–97] are also involved in the development of IIMs, mainly acting as APCs and a source of pro-inflammatory cytokines to activate the T cell response and mediate tissue inflammation [98].

3.3. Changes in the target tissue

During active phases of PM/DM, muscle fibers and endomysial capillaries experience pathological alteration. Firstly, MHC-I is ubiquitously upregulated in polymyositis, even on muscle fibers that are remote from the site of inflammation [99], which is probably induced by cytokines secreted by activated T cells [51,55]. In addition, muscle fibers in PM also express co-stimulatory factors including ICOSL, CD40L, CD80 and to form tight immune synapses with T cells [100,101]. Overexpression of myxovirus resistance A (MxA), a type I interferon–inducible protein, is observed in a perifascicular distribution or sometimes diffusely in biopsied muscle specimens of DM [91], and may help with differential diagnosis [102]. On the other hand, Fas antigen on muscle fibers and FasL on autoinvasive CD8-positive T cells are identified, but the Fas-FasL-dependent apoptotic process is not functionally normal [103,104]. Expression of the anti-apoptotic molecules BCL2, Fas associated death domain-like interleukin-1-convertingenzyme inhibitory protein (FLICE), and human IAP-like protein (hILP) may confer resistance of muscle to Fas mediated apoptosis [103,105,106].

4. Clinical features

Both PM and DM present with a varying degree of muscle weakness, usually developing slowly over weeks to months, but acutely in rare cases [107]. The weakness is relatively symmetric, predominantly proximal and unassociated with sensory loss or ptosis with sparing of extraocular muscles which are characteristics of myasthenia [3,107]. In the late stages of PM and DM, distal muscle weakness which affects fine motor movements can occur. In contrast, this feature is an early and prominent finding in sIBM [108].

In PM and DM, the neck extensor muscles may also be involved, causing difficulty in holding up the head and rarely causing a dropped head syndrome (DHS) [109]. Primary weakness of the diaphragm and accessory muscles, or pharyngeal muscles in advanced cases, may contribute to respiratory insufficiency or dysphagia, nasal speech, hoarseness, nasal regurgitation, and aspiration pneumonia [110,111]. The tendon reflexes are usually preserved but may be absent in severely weakened or atrophied muscles. Myalgia occurs in less than 30% patient with polymyositis and dermatomyositis [112].

There are many diseases whose symptoms resemble PM or DM, increasing the possibility of misdiagnosis and introducing additional challenges in classification and management, especially in PM. Patients with anti-synthetase autoantibodies may carry a diagnosis of DM or PM. Presenting symptoms include myalgias, muscle weakness, and a combination of interstitial lung disease (ILD), Raynaud phenomenon, seronegative arthritis of the distal joints, fever, mechanic's hands, and a skin rash that is different from the heliotrope erythema typically seen in DM [113–115]. PM may be diagnosed erroneously in DM patients who present with isolated proximal muscle weakness and develop the rash months later [116]. sIBM has been shown as the most common disease misdiagnosed as PM, whereby sIBM is suspected retrospectively in patients who do not respond to therapy for polymyositis. PM may also be diagnosed incorrectly in cases of NAM, overlap syndrome associated with a connective tissue disease, muscular dystrophies, myalgia syndromes, toxic and endocrine myopathies, and Kennedy's disease (KD) [2,107,117–119]. In chronic DM, patients may suffer from fasciitis and thickening of the skin, which can also occur in patients with eosinophilia-myalgia syndrome, eosinophilic fasciitis, or macrophagic

myofasciitis [120,121].

4.1. Polymyositis

PM is frequently misdiagnosed, as it lacks a unique clinical phenotype and remains a diagnosis of exclusion [3,122]. PM is best defined as a subacute proximal myopathy that evolves muscle weakness over weeks to months, affects adults but rarely children, and excludes those who have a rash, a family history of neuromuscular disease, exposure to myotoxic drugs (e.g., statins, penicillamine, and zidovudine), involvement of facial and extraocular muscles, endocrinopathy, or a clinical phenotype of sIBM [3,5]. PM mimics many other myopathies and may also be diagnosed incorrectly in cases of DM, sIBM, NAM, overlap syndrome associated with a connective tissue disease, muscular dystrophies, myalgia syndromes, or toxic and endocrine myopathies [118,122–124].

4.2. Dermatomyositis

DM is identified by a characteristic rash accompanying or preceding subacute muscle weakness [3]. About 6% of patients have no or poorly recognized skin involvement. However, histologic feature of the muscular biopsy sample may be helpful in diagnosing DM. In these cases, where there is no skin involvement, the condition is termed dermatomyositis sine dermatitis [125]. Up to 20% patients with cutaneous features of DM and typical histopathologic features on muscle biopsy but without clinical muscle weakness for more than 6 months are categorized as amyopathic dermatomyositis (ADM) [126,127]. The skin manifestations of DM include a violaceous eruption (Gottron's papules) on the knuckles, which is pathognomoic for DM; a characteristic periorbital heliotrope (blue–purple) rash with edema; an erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (in a V-sign), and back and shoulders (in a shawl sign); and, which may evolve into a scaly discoloration. Dilated capillary loops at the base of the fingernails, irregular and thickened cuticles, and cracked palmar fingertips ("mechanic's hands") are characteristic of DM. These lesions are photosensitive and are commonly pruritic.

4.3. JDM

In children, DM is the most frequent inflammatory myopathy while PM is very rare [128]. DM in children is referred to as Juvenile Dermatomyositis (JDM).

The average age of onset of JDM is approximately 7 years old and the female-to-male ratio is about 2:1 [129–131]. The pathogenesis and major clinical and autoantibody phenotypes in children are similar to those in adults. Skin rash, consisting of a heliotrope eyelid discoloration and Gottron's papules, and proximal muscle weakness are the most common manifestations of JDM, while lesions include cutaneous calcinosis, which develops over pressure points, occurs more commonly in JDM [132]. Other lesions that occur more commonly in JDM include subcutaneous calcifications, sometimes extruding to the surface of the skin and causing ulcerations and infections. Rare dermatologic findings include non-scarring alopecia, erythroderma, vesiculobullous lesions, leukocytoclastic vasculitis, and livedo reticularis [3,5,127,132].

Other organ systems including the gastrointestinal tract, lungs, heart, articular, visual, and nervous system can also be involved [131], although the prevalence of ILD and cancer is different between JDM and adult DM. An autoantibody to a 155 kDa protein with a second weaker 140 kDa band, called anti-p155/140, has been found in sera of 23–29% of JDM cases and is associated with a risk of more severe skin involvement and generalized lipodystrophy [133–135]. The serological and genetic differences between adult DM and JDM may provide insights into the pathogenic mechanisms that underlie their clinical differences [136].

4.4. Other extramuscular manifestations and involvements

IIM patients exhibit many other extramuscular manifestations. As a result, diagnosis and the evaluation for other organ system involvement is imperative towards determining the optimal treatment strategy for PM and DM.

4.4.1. Cardiac abnormalities

In adult onset IIM, cardiovascular complications represent a major cause of clinical deterioration and death [137]. Cardiac involvement may include inflammation of the myocardium, accelerated coronary atherosclerosis, angina, dysrhythmias and more [138–140]. Heart abnormalities may occur during any phase of PM/DM, even when PM/DM is in remission [141]. According to a retrospective analysis of adults PM/DM patients in British Columbia, there is an increased risk of myocardial infraction (MI) but not of stroke in patients with PM/DM compared with a control cohort [142]. Electrocardiograms (ECG), echocardiogram (ECHO), cardiac magnetic resonance (CMR) imaging and cardiac enzymes analysis may be helpful to diagnose subclinical heart complications [143–145]. In addition, anti-mitochondrial antibodies (AMA) may be associated with cardiovascular involvement in IIM [146]. The efficacy of glucocorticoids and immunosuppressants in the treatment of cardiac complications is undetermined [147,148].

4.4.2. Pulmonary symptoms

Interstitial lung disease (ILD) is a common extramuscular manifestation of myositis. PM/DM patients with accompanying ILD have poorer prognosis than those without [149,150] DM-ILD usually demonstrates a more severe course with a poorer prognosis that is more resistant to treatment than PM-ILD [151,152]. The characteristics of PM/DM-ILD include a non-productive inspiratory cough and dyspnea [153], lymphocyte or neutrophil alveolitis in bronchoalveolar lavage (BAL), and interstitial pneumonia in lung biopsy samples [154]. High-resolution computed tomography (HRCT) and pulmonary function tests (PFT) are important for diagnosis of lung involvement in PM and DM [155,156].

Recently, two types of myositis-specific autoantibodies (MSAs), anti-aminoacyl transfer RNA synthetases (ARS) and anti-CADM-140 (MDA-5/IFIH1) antibodies, have been shown to be associated with ILD in myositis, suggesting separate clinical and serological phenotypes [157]. For example, numerous reports have indicated a higher prevalence of rapidly progressive ILD with ADM and anti-MDA-5 antibodies, with many patients being refractory to immunosuppressive therapy [158–160]. In the case of anti-Jo-1 associated ILD, the presence of high levels of anti-Ro52 antibodies predicts a more severe acute-onset disease and non-responsiveness to immunosuppressive treatment [161,162].

4.4.3. Malignancy

An association between PM/DM and malignant disease has been reported and confirmed. Studies show that DM is strongly associated with ovarian, lung, pancreatic, stomach, colorectal cancers, and non-Hodgkin lymphoma [163], while PM is associated with an increased risk of non-Hodgkin lymphoma, lung and bladder cancers [164–168]. JDM has a 16-fold increased risk for hematopoietic or lymphoid malignancy [169]. In addition, malignant disease is more common in older patients (>50 years of age) and may occur before the onset of PM/DM, concurrently with PM/DM, or after the onset of PM/DM. However, the risk of malignant disease is highest shortly after myositis diagnosis in both DM and PM [164,169,170].

Scientists have assessed the diagnostic values of serum tumor markers for the detection of solid cancer in PM/DM patients and found that carcinoembryonic antigen CA125 and CA19-9 assessment may be useful markers [171]. On the other hand, there are several examples of tumor-associated immune responses that target seemingly unrelated tissues in a predictable fashion, which has been extensively described in the autoimmune paraneoplastic neurological disorders (PNDs) [172]. Compared to IIM without cancer, cancer associated myositis (CAM)

shows different clinical and immunological features, as well as antigen expression [173,174]. Absent myositis-specific/associated autoantibodies and positive anti-155/140 antibody, anti-SAE1, anti-TIF1-γ and anti-NXP2 antibodies are associated with a high risk of CAM [175–177]. Moreover, the gene expression profile of IIM with malignancy is similar to that of DM rather than PM, which suggests that humoral immunity plays a significant role in PM/DM [178].

4.4.4. Other manifestations

Several studies show an increased prevalence of celiac disease in IIM [179,180]. Renal involvement develops in about one fifth of IIM patients [181–183]. PM and DM are frequently associated with systemic sclerosis and mixed connective tissue disease in the context of an overlap syndrome [184,185]. It has also been reported that several cases of JDM have been complicated by systemic capillary leak syndrome (SCLS), a rare, life-threatening disorder characterized by severe hypotension, hypoalbuminaemia and hemoconcentration [186]. Lipodystrophy, hypertriglyceridemia and insulin resistance have also been associated with JDM [187,188].

5. Prognosis

A United States study in 2012 of 160 p.m./DM patients demonstrated a 10 year survival rate of 62% [189]. Deaths are mainly caused by cardiac (22%) and pulmonary (22%) complications, infections (15%), and cancer (11%) [189]. Prognostic factors including gender, age at time of diagnosis, presence of Raynaud phenomenon, ILD, dysphagia, respiratory muscle involvement and cardiac involvement at any time in the clinical course affect prognosis [137], while the prognostic role of autoantibodies needs further long-term investigation. The long-term data for JDM are still scarce. Compared to age-matched controls, adults who had JDM showed reduced quality of life and reduced fitness measured by maximal oxygen uptake as a measure of muscle function [190,191].

6. Diagnosis and classification

Bohan and Peter's diagnostic criteria, proposed in 1975, have been widely accepted [1,192]. Patients complaining about muscle weakness, fatigue and myalgia, with or without skin rash should be suspected as having PM or DM. Table 2 listed the Bohan and Peter's diagnostic criteria of PM/DM with the exclusion of family history of neuromuscular disorder, endocrine or neurogenic diseases, myotoxic drug exposure, muscular dystrophies and metabolic myopathies, sIBM, NAM or infection [1,192,193]. Because of studies with undersized patient cohort and potentially erroneous disease classification, these criteria are not perfect, and often fail to rule out IBM.

In 2003, Dalakas and Hohlfeld supplemented the existing criteria with pathologic features [3]. First, they reiterated the crucial role of the muscle biopsy test, and proposed the following: primary inflammation with the CD8/MHC-I complex and no vacuoles for definite PM, ubiquitous MHC-I expression but no $CD8^+$ cell infiltrates or vacuoles for probable PM, perifascicular, perimysial or perivascular infiltrates, perifascicular atrophy and rash present for definite DM; no rash present for probable DM. In addition, ADM is diagnosed when a rash is present but biopsy findings are nonspecific or are diagnostic for DM, and no weakness is present.

In the MSG and ENMC international workshop in 2003, many neurologists, rheumatologists, and statisticians worked together to propose classification criteria for IIMs [2], as shown in Table 3. More importantly, this workshop provides information on how to apply these criteria to each category of myositis, including definite and probable PM/DM, ADM, possible DM sine dermatitis, non-specific myositis and NAM. At the same time, this workshop also pointed out the unmet needs in treatment due to difficulties in the study design and the low incidence and prevalence of patients. The workshop also promoted the development of valid, sensitive, and reliable outcome measures for (randomized controlled trial) RCTs in myositis.

In recent decades, muscle immunopathology, myositis specific autoantibodies testing, and new techniques of muscle imaging such as contrast-enhanced ultrasound or Magnetic Resonance Imaging (MRI) have been used in the diagnosis of patients with IIM, contributing to improved diagnostic capability [125].

6.1. Clinical history and physical examinations

Obtaining a clinical history is crucial and should include information on disease onset, pattern of presentation, and possible inciting or environmental factors. Environmental factors including recent infections, drugs (over-the-counter, prescription or recreational), work exposures, diet and nutritional supplements. Family history can help determine the potential genetic contributors to the myopathy. In addition, a good history should also elicit information regarding pattern of weakness, including distal versus proximal, symmetric versus asymmetric, or bulbar involvement. This portion of the history can be confirmed or supported by physical findings. Validated patient/parent questionnaire of activities of daily living (Health Assessment Questionnaire, HAQ/childhood Health Assessment Questionnaire CHAQ) and validated observational tools of function, strength and endurance (Childhood Myositis Assessment Scale, CMAS) are recommended by the International Myositis Assessment and Clinical Studies Group (IMACS) [194,195].

6.2. Blood tests

6.2.1. Muscle enzymes

When the muscles are damaged, muscle enzyme elute from muscle fibers leading which can be detectable in plasma or serum. Serum

Table 2
Bohan and peter criteria for polymyositis and dermatomyositis.

Cretirion	Polymyositis		Dermatomyositis		Details
	Definite	Probable	Definite	Mild or early	
Muscle strength	Myopathic muscle weakness	Myopathic muscle weakness	Myopathic muscle weakness	Seemingly normal strength	Symmetrical and progressive weakness of the proximal limb-girdle muscles
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic or nonspecific	Short duration, low amplitude polyphasic units; fibrillations, complex repetitive discharges; positive sharp waves
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 10-fold)	Creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, aldolase
Muscle-biology findings	Diagnostic for this type of inflammatory myopathy	Nonspecific myopathy without signs of primary inflammation	Diagnostic	Nonspecific or diagnostic	Perivascular, interfascicular or endomysial inflammatory infiltration; phagocytosis, necrosis, and regeneration of muscle fibers; capillary obliteration and endothelial damage
Rash or calcinosis	Absent	Absent	Present	Present	Heliotrope rash and Gottron's sign/papules

Table 3
Elements of the classification criteria for the IIM (except sIBM) approved by the MSG and the 119th ENMC workshop.

Clinical criteria	Inclusion criteria	a) Adult onset, or in childhood in DM and nonspecific myositis b) Subacute or insidious onset c) Pattern of weakness: symmetric proximal > distal, neck flexor > neck extensor d) Rash typical of DM: heliotrope periorbital edema; Gottron's papules/sign, scaly if chronic, at metacarpophalangeal and interphalangeal joints and other bony prominences; V-sign and shawl sign
	Exclusion criteria	a) Clinical features of IBM[a] b) Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness c) Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscular dystrophy or proximal motor neuropathies
Electromyography	Inclusion criteria	a) Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges b) Morphometric analysis reveals the presence of short duration, small amplitude, polyphasic MUAPs
	Exclusion criteria	a) Myotonic discharges that would suggest proximal myotonic dystrophy or other channelopathy b) Morphometric analysis reveals predominantly long duration, large amplitude MUAPs c) Decreased recruitment pattern of MUAPs
Other laboratory criteria	a) MRI: diffuse or patchy increased signal within muscle tissue on STIR images b) Myositis-specific antibodies detected in serum c) Elevated serum creatine kinase level	
Muscle biopsy	a) Endomysial inflammatory cell infiltrate (T-Cells) surrounding and invading non-necrotic muscle fibers b) Endomysial $CD8^+$ T-cells surrounding, but not definitely invading non-necrotic muscle fibers, or ubiquitous MHC-I expression c) Perifascicular atrophy d) MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells, or MHC-I expression of perifascicular fibers e) Perivascular, perimysial inflammatory cell infiltrate f) Scattered endomysial $CD8^+$ T-cells infiltrate that does not clearly surround or invade muscle fibers g) Many necrotic muscle fibers as the predominant abnormal histological feature. Inflammatory cells are sparce or only slight perivascular; perimysial infiltrate is not evident. MAC deposition on small blood vessels or pipestem capillaries may be seen, but tubuloreticular inclusions in endothelial cells are uncommon or not evident. h) Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM i) MAC deposition on the sarcolemma of nonnecrotic fibers and other indications of muscular dystrophies with immunopathology	

Modified from Ref. [2].
[a] Clinical features of IBM is reviewed in Ref. [264].

Creatine Kinase (CK) level is the most sensitive but not specific indicator. The CK level does not normally correlate with the severity of the symptoms among different patients, but can reflect changes in disease activity within an individual patient. Elevated CK levels range from 5 to 50-fold above normal in PM. 70–80% of DM patients will have up to 50-fold levels while the rest will have normal CK levels [196]. CK levels can be extremely high and reach 100-fold of normal in NAM, whereas they are often normal or only mildly elevated in sIBM patients [197]. Other identified elevated muscle enzymes include lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are also markers of liver injury, and aldolase, which is a marker of muscle cell degeneration or cell membrane damage. Other serum inflammatory biomarkers such as Erythrocyte Sedimentation Rate (ESR) and C-reactive protein may also be increased during the active phase [198]. Elevated Interleukin-1RA (IL-1RA) is considered to be a diagnostic clue in PM and DM, and can be found in most patients even in the absence of CK elevation [199].

6.2.2. Antibodies

Autoantibodies associated with IIM are subdivided into myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA), as shown in Table 4. MSAs are found in approximately 50–60% of patients with IIM while MAAs are also found in other autoimmune diseases [200]. As is the case in other autoimmune diseases, the pathogenic role of the antibodies in PM and DM is unclear, although some appear to be specific for distinct clinical phenotypes and HLA-DR genotypes. The MSAs might be divided into three broad groups (1) anti-tRNA synthetases, (2) anti-signal recognition particle (anti-SRP), and (3) other antibodies against cytoplasmic or nuclear components involved in the regulation of protein synthesis and translocation, gene transcription, and viral recognition including anti-Mi-2 anti-PM-Scl and anti-CADM-140 [201,202].

6.3. Muscle imaging

6.3.1. Magnetic Resonance Imaging

MRI is a very useful imaging tool of choice for both assessment of disease activity and selection of the biopsy site, providing a detailed anatomic view of the extent of muscle involvement [203]. Muscle necrosis, degeneration, and inflammation can be detected by MRI and are characterized by increased signal intensity on short tau inversion recovery (STIR) [204]. T1-weighted images are useful for detecting muscle damage and for loss of volume and fatty replacement whereas T2-weighted images are useful for distinguishing the fatty infiltration and edema seen in active muscle inflammation. The latter correlates with disease activity [205–208]. It is recommended by new diagnostic criteria that MRI can be used to evaluate JDM in order to avoid electromyography (EMG) or muscle biopsy [209]. Although the edema in skeletal muscles on MRI is not specific for myositis, it is more commonly seen in myositis in comparison to non-inflammatory myopathies.

6.3.2. Muscular ultrasound

Ultrasound, specifically doppler sonography, contrast-enhanced ultrasound, and sonoelastography may be also be used to differentiate between normal and pathologic muscle [210], but its sensitivity and negative predictive value for diagnosis remain low compared to MRI. Acute muscular inflammation is characterized by normal or increased size, low echogenicity, and elevated perfusion of affected muscles, whereas in the chronic disease stage, muscle size and perfusion are reduced and echogenicity is increased. Moreover, being widely available and cheap, muscular ultrasound is a useful tool in the follow-up of muscle lesions especially when MRI is not available, and it can reveal complications such as fibrosis, cystic hematomas, or myositis ossificans [211].

6.4. EMG

The characteristic EMG features of myositis patients are: (1) increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic or complex repetitive discharges, (2) polyphasic motor unit action potentials (MUAPs) of short duration and low amplitude, (3) early recruiting MUAPs [107]. Although it is nonspecific, abnormalities may be observed in 70–90% of patients. The additional value of EMG includes identifying the highest yield biopsy sites and assessing response to therapy.

Table 4
Autoantibodies in PM/DM.

Antibodies		Target antigen and function	Clinical association	References
Myositis-specific autoantibodies (MSAs)	Anti-Mi-2	DNA helicase/Transcription regulation (component of the NuRD complex)	15–30% (DM, associated with a favorable prognosis and suggestions of environmental trigger in adult DM)	[265–267]
	Anti-CADM-140 (MDA5)	MDA5/Innate immune response against viruses	20% (DM, associated with ADM and aggressive ILD)	[268,269]
	Anti-SAE	SUMO-1 Activating Enzyme 1/Posttranslational modifications	3–8% (adult DM, associated with rash)	[162,270]
	Anti-p155/140	TIF1-γ/Nuclear transcription	20–30% (associated with malignancy in adult and calcinosis in JDM)	[271–273]
	Anti-MJ (NXP-2)	Nuclear matrix protein/p53-mediated cell senescence	2% (adult DM, associated with malignancy)	
	Anti-(HMGCR)	HMG-CoA reductase/Cholesterol biosynthesis	7% (adult PM, associated with poor therapy response in JDM)	[274,275]
	Anti-SRP	SRP/Protein translocation across the endoplasmic reticulum	4–6% (adult PM, associated with acute and severe proximal weakness, dilated cardiomyopathy, ILD, and steroid resistance)	[86,276]
	Anti-ARS	aminoacyl-tRNA synthetases/Protein synthesis	30–40% Predictors of antisynthetase	[277,278]
	Anti-Jo1	Histidyl	20–30% syndrome	
	Anti-PL-7	Threonyl	2–5%	
	Anti-PL-12	Alanyl	2–5%	
	Anti-EJ	Glycyl	2–5%	
Myositis-associated autoantibodies (MAAs)	Anti-KL6	Mucin-like glycoprotein (on alveoli or bronchial epithelial cells)	Patients with ILD	[3]
	Anti-Ro/SSA	Ro52 and RO60	9–19% (common in Sjögren syndrome)	[162]
	Anti-U1RNP	U1-small nuclear ribonucleic proteins/pre-messenger RNA processing	3–8% (common in overlap condition, good prognosis)	[278,279]
	Anti PM/Scl	75-kDa and 100-kDa subunits of the nucleolar exosome complex	15% (DM, associated with scleroderma in PM)	[280,281]
	Anti-Ku	70- and 80-kDa Ku heterodimers	1–3% (common in overlap syndrome, require of high-dose corticosteroids)	[282]

6.5. Muscle biopsy

Although the pivotal role that muscle biopsy plays in the diagnosis of IIM is agreed upon by many investigators, it was not until 1984 that histopathological features were clearly established by Arahata and Engel [212]. Although very specific and important, muscle biopsy is not regarded as obligatory for diagnosis when typical features such as skin changes or specific autoantibodies are present and are consistent with clinical manifestations. Muscle histology allows distinguishing 4 main subtypes of IIM on the basis of distinct immunopathologic features: DM, PM, s-IBM, and NAM.

In PM, perivascular inflammation is most typically concentrated in multiple foci within the endomysium. $CD8^+$ T cells invading healthy-appearing, nonnecrotic muscle fibers expressing MHC class I antigen are typically involving the fascicles. In DM, histopathology typically shows perivascular inflammation which is most prominently located in the interfascicular septae or the periphery of the fascicles. The muscle fibers undergo necrosis and phagocytosis, leading to hypoperfusion and perifascicular atrophy, which is characterized by layers of atrophic fibers at the periphery of the fascicles with perivascular and interfascicular infiltrates. Capillary deposition of the complement C5b-9 MAC with the presence of endothelial tubuloreticular inclusions and microinfarcts can also be detected [64,107,122,213,214]. In contrast, vacuolated muscle fibers, degeneration/regeneration areas, necrotized/phagocytized fibers, β-pleated-sheet amyloid inclusions, and phosphorylated tau are typically found in biopsies of sIBM, while NAM is characterized by abundant necrotic and regenerative fibers that contrast with modest inflammation consisting of macrophage rather than T cells infiltration [6,215].

7. Treatment & management

A clinical misdiagnosis attributed to cursory examinations or erroneous interpretation of the biopsy usually leads to unnecessary, inappropriate or delayed therapies. For example, dermatomyositis responds better to conventional treatment than polymyositis, and some cases of "polymyositis unresponsive to therapies" should be suspected as being sIBM, NAM or other myopathies [216]. Currently, the primary goal of therapy should be an objective increase in strength and daily activities, as well as an improvement in systemic manifestations. Decreased serum muscle enzymes may be observed after treatment in the absence of an improvement in muscle strength, so called "chemical improvement". Unfortunately, some clinicians may fall into the habit of "chasing" or "treating" the CK concentration instead of the muscle weakness, ignoring the fact that the treatment they are using may be clinically ineffective. The main concern about drug therapy in IIMs is the lack of controlled trials and the absence of standardized outcome measures to capture meaningful changes to identify correlations between disability and quality of life [53,217,218]. When considering treatment options for patients with IIMs, great care should be taken to ensure that optimal therapies are being used which can positively impact patient quality of life.

The mainstay of therapy for DM and PM consists of immunosuppression, physical therapy, monitoring for adverse events from medications, and prevention of complications [53]. The most commonly used pharmacological therapies in clinical practice are listed in Table 5.

7.1. Immunosuppression medications

7.1.1. First-line therapy

Glucocorticoids remains the first-line therapy for IIMs with a standard oral prednisone dose of 1 mg per kilogram of body weight (high dose, up to 100 mg per day). It should be noted that this choice of drug is based on experience and not on placebo controlled trials [53,219]. A clinical trial found no difference in efficiency between pulsed high-dose oral dexamethasone and daily prednisolone as first line treatment of IIMs, although dexamethasone showed substantially fewer side-effects [220]. In patients with rapidly worsening disease, intravenous methylprednisolone administration is preferable at a dose of 1000 mg per day for 3–5 days before starting treatment with oral glucocorticoids. Depending on efficacy and side effects, the daily dose is slowly reduced or switched to

Table 5
Therapeutic regimens for PM/DM.

Patients condition	Agents	Typical dose	Side effect and toxicities
New-onset disease	Prednisone	1 mg per kilogram, up to 100 mg per day for 4–6 weeks (orally); taper to alternate days	Increased susceptibility to infection, osteoporosis, hypertension, diabetes, weight gain, steroid-induced myopathy, mood changes, skin fragility, avascular necrosis, glaucoma
Late or severe disease onset, rapidly worsening	Methylprednisolone	1000 mg per day for 3–5 days (IV), then switch to oral regimen	
Steroid refractory	Intravenous Immunoglobulin	2 g/kg total dose given over 2–5 days (1 g/kg/day over 2 days or 0.4 g/kg/day over 5 days), repeated monthly for at least 3 months, intravenously	Flu-like symptoms, myalgias, fever, headache, fluid overload, rash, aseptic meningitis, caution in patients with cardiac conditions, risk of renal failure or thrombosis
Steroid-sparing regents	Azathioprine	2–3 mg/kg/day (orally)	Fever, abdominal pain, nausea, vomiting, anorexia; combination with allopurinol increased myelosuppression and hepatoxicity; thiopurine methyltransferase activity may need to be checked in certain patients prior to initiation of medication or in those with poor reaction to treatment
	Methotrexate	15–25 mg/week (orally), should be given with folate 1 mg/day (IV);	Hepatotoxicity, ILD (caution in those with anti- Jo-1 antibody positivity), interstitial pneumonitis, myelosuppression, renal toxicity, alopecia, stomatitis, oncogenicity, teratogenicity
	Mycophenolate mofetil	1–1.5 mg twice daily, 500 mg twice daily in renal impairment (orally)	Diarrhea, myelosuppression, tremors, hypertension
	Tacrolimus	2–3 mg twice daily (orally)	Increased susceptibility to infection, lymphoma, alopecia, skin erythema, pruritis, constipation, diarrhea, nausea, anemia, leukocytosis, thrombocytopenia, headache, hypertension, paresthesia, tremor, renal failure
	Cyclophosphamide	1–2 mg/kg/day (orally), or 1 g/m2 monthly (intramuscularly)	Gastrointestinal upset, alopecia, risk of malignancy, hemorrhagic cystitis, teratogenicity, sterility, increased risk of infection
	Cyclosporine	3–4 mg/kg/day (orally)in two divided doses, then increase up to 6 mg/kg/day	Hypertension, renal failure, gingival hyperplasia, Gastrointestinal upset, hypertrichosis, oncogenicity, tremor, risk of infection
Steroid refractory	Rituximab	1 g (IV), repeat in 2 weeks; then subsequent doses 6–9 months after second dose	Fever, nausea, infection susceptibility, rare infusion reactions, rare progressive multifocal leukoencephalopathy
No objective improvement	If diagnosis is reconfirmed, recommend participation in a research trial (candidates include eculizumab, alemtuzumab, tocilizumab (anti–IL-6), anti–IL-17, and anti– IL-1β and so on)		

Modified from Refs. [4,5].

an alternate-day program slowly over several weeks, until the lowest possible dose that controls the disease is reached.

Some clinicians claim that other steroid sparing agents also should be used [53,221]. Indeed, if the patient is unresponsive to steroids, and objective signs of increased strength and ability to perform activities in daily living in months are not observed, tapering should be accelerated so that treatment with an alternate agent can be initiated. Importantly, patients with other co-morbidities such as hypertension, diabetes, osteoporosis, and obesity, which will be exacerbated by corticosteroid use, should be started on a second-line agent early and subsequently have their prednisone tapered to a minimally effective dose. Adverse events need to be carefully monitored while on chronic high dose corticosteroids. Treatment for bone and liver complications and gastric mucosa protection should be considered to help minimize the adverse side effects of steroids.

7.1.2. Other immunosuppressive medications

Studies have demonstrated the efficacy of glucocorticoids in improving muscle strength and achieving prolonged treatment-free remissions [222–224]. However, there is still a high percentage of patients with IIM who fail to respond completely to glucocorticoids alone [225]. Intravenous immune globulin therapy has been shown to be effective in severe and rapidly progressive or refractory PM and DM in several clinical trials [219,226,227]. Azathioprine (AZA), a derivative of 6-mercaptopurine, is administered orally at a dose of 2–3 mg/kg daily and is usually effective after 4–8 months, according to a small number of case series or case studies [228–231]. Methotrexate (MTX), an antagonist of folate metabolism, has been reported to be used in steroid-refractory PM first in 1968 [232] and then in other studies [230,233,234]. MTX is often given orally, starting at 3 doses of 2.5 mg every 12 h weekly for the first 3 weeks, with a gradual increase by 2.5 mg per week up to a total of 15–20 mg weekly [235]. Mycophenolate mofetil (MMF), a morpholinoethyl ester of mycophenolic acid that blocks de novo purine synthesis, is administered orally at a dose of up to 3 g per day, but it can take up to 2–3 months to see the benefits of treatment. MMF is well tolerated although it may be expensive [218]. Cyclosporine, which affects T-cell-mediated immunity by inhibiting transcription of the *IL2* gene, is given at doses of 150 mg twice a day (not more than 5 mg/kg per day). Cyclosporine is useful in newly diagnosed PM and DM although it has significant side effects [127]. Each of these immunomodulating medicines exhibits efficacy at different stages of disease or in different complications and are associated with significant side effects, including bone marrow suppression and infections, so they need to be used under careful considering and monitoring.

7.2. New biological therapies

In refractory PM/DM, biological agents which have been approved for the treatment of other immune diseases may be considered as experimental treatment options.

7.2.1. Rituximab

Rituximab, an anti-CD20 antibody, causes depletion of the circulating B cells for at least 6 months [236]. It is reported that Rituximab administration can be effective for some patients with PM and DM who are resistant to other therapies [237–241]. It has also been reported that rituximab may be helpful in PM/DM-related ILD [242]. It follows that biologics directed against B cells should theoretically be helpful in treating autoimmune diseases with MSAs, and indeed there is research demonstrating that Rituximab is more effective in the presence of an

anti-synthetase, anti-Mi-2, or other autoantibody, with a shorter time to improvement, compared to the autoantibody negative subset [243].

7.2.2. Tumor necrosis factor inhibitors

TNF inhibitors (Infliximab, Adalimumab and Etanercept) have been approved to treat autoimmune disorders including rheumatoid arthritis (RA), juvenile idiopathic arthritis and psoriatic arthritis. Anecdotal reports suggest that TNF inhibitors can be helpful in the treatment of a subset of patients with PM or DM [244,245], although other reports show no such benefit and have even been reported to induce flares. It should be noted that treatment of autoimmune diseases with TNF inhibitors has been associated with the development of new autoimmune diseases, and there are numerous case reports of IIMs induced by anti-TNF agents as well [246,247]. In general, anti-TNF therapy is not routinely used in myositis and further studies are needed to obtain more data on efficacy and safety.

7.2.3. Newer agents

Other agents targeting cells or molecules that are involved in autoimmune diseases have been used in the treatment of PM and DM, and are described predominantly as case reports only. These regents and their mechanisms include Alemtuzumab, Efalizumab, tacrolimus and rapamycin, which target T-cell intracellular signaling pathways. Alemtuzumab is a humanized anti-CD52 monoclonal antibody, which interferes with T-cell signaling and has shown to be effective in improving muscle strength in a case of refractory PM [248] and has achieved comparable immune ablation compared to a pre-hematopoietic stem cell transplantation (HSCT) conditioning regimen in juvenile PM case [249]. Other strategies include targeting B-cell growth factors by inhibiting B-cell activating factor (BAFF) and a related ligand, APRIL, targeting complement with Eculizumab, a monoclonal antibody against C5, and targeting cellular adhesion and T-cell migration with Natalizumab, a monoclonal antibody directed against the α4β1 integrin VLA4 [53,127,218,250]. The involvement of activated complement, T cells, B cells, cytokines, adhesion molecules, and transmigration molecules in the pathogenesis of PM and DM justifies the use of several new biologic agents that target specific molecules, but there is still a need for further clinical studies to evaluate efficacy and safety.

7.3. Nonpharmacological treatment

Nonpharmacological therapies must also be integrated into the care of patients with myositis. Exercise and physical therapy are important components of treatment for patients with IIM. These therapies are safe and may improve aerobic capacity and muscle strength [251–253]. In addition, diet and lifestyle changes and modifications can have a positive effect. The role of dietary supplementation hitherto in the treatment of IIMs is limited. However it has been shown in a clinical trial that patients with DM or PM improved significantly with oral creatine supplements in conjunction with exercise as compared with exercise alone, based on functional performance times and better performance in laboratory examinations [254]. In addition, dietary modifications such as a low-fat, low-carbohydrate, and low-salt diet need to be undertaken by patients receiving corticosteroids to minimize effects of weight gain, hypertension, hyperglycemia and edema. Calcium (1 g/d) and vitamin D (400–800 IU/d) supplementation to decrease the risk of osteopenia is also recommended [53]. Thirdly, assistive devices, home modifications, precautions for aspiration in patients with severe dysphagia and emotional support may be helpful for those patients who suffer from more rapid disease progression and weakness [53].

8. Conclusion

Unmet needs or challenges in PM and DM include better diagnostic algorithms and more effective and safe treatment modalities. More specifically, how to improve diagnostic precision to avoid misdiagnosis or delayed treatment due to the uncertainty of excluded diagnosis is critical. In addition, a better understanding of the disease pathogenesis and the progression of disease may help to guide future treatment and research strategies Great strides have been made in advancing the diagnosis and treatment of other autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and Crohn's disease, which regretfully have not yet been fully seen in patients with IIMs. The incidence and prevalence of PM/DM is fairly low, and as a result, the amount of basic and clinical research performed is much less than other autoimmune diseases, and unified and authoritative diagnosis criteria and management outlines are not frequently updated. In conclusion, a great deal of international cooperation still needs to be realized in order to improve the lives of patients suffering from IIMs.

9. Contributions

Shu-Han Yang and Christopher Chang wrote the manuscript. Shu-Han Yang made the tables. Christopher Chang and Zhe-Xiong Lian edited the manuscript.

Declaration of competing interest

The authors have declared that no conflict of interest exists.

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