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Diagnosis, pathogenesis and treatment of myositis: recent advances

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Summary

Dermatomyositis (DM), polymyositis (PM), necrotizing myopathy (NM) and inclusion body myositis (IBM) are four distinct subtypes of idiopathic inflammatory myopathies – in short myositis. Recent studies have shed some light on the unique pathogenesis of each entity. Some of the clinical features are distinct, but muscle biopsy is indispensable for making a reliable diagnosis. The use of magnetic resonance imaging of skeletal muscles and detection of myositis-specific autoantibodies have become useful additions to our diagnostic repertoire. Only few controlled trials are available to substantiate current treatment approaches for myositis and hopes are high that novel modalities will become available within the next few years. In this review we provide an up-to-date overview of the pathogenesis and diagnostic approach of myositis. We aim to present a guide towards therapeutic and general management.

Keywords: muscle immunology/disease, myositis, neuroimmunology

Introduction

Idiopathic inflammatory myopathies – in short myositis – include dermatomyositis (DM), polymyositis (PM), necrotizing myopathy (NM) and inclusion body myositis (IBM). They all present with muscle weakness. Diagnosis is based on the clinical examination (distribution of paresis) in combination with laboratory values, including creatine kinase (CK) and autoantibodies, electromyography (EMG) and the histopathology of the skeletal muscle. The use of magnetic resonance imaging (MRI) of the skeletal muscle is not only helpful to identify an adequate muscle for biopsy, but also to demonstrate the pattern of affected muscles beyond clinical appearance, which helps to exclude, for example, muscular dystrophies. While DM, PM and NM mainly respond well to treatment with immunosuppressants, IBM is usually resistant to these drugs, and only in few patients may immunoglobulins display a temporary beneficial effect.

Dermatomyositis (DM)

The incidence and prevalance of DM are 1·4 and 5·8 cases among 100 000 people in the United States [1]. It shows a female preponderance and a higher prevalence among older people. As juvenile DM (JDM), it can occur in children with a prevalence of 3·2 among 1 million children in the United Kingdom and is more common among girls [2].

Patients present with a symmetric proximal muscle weakness that develops within weeks or months, together with

typical erythematous changes [3]. The skin changes can also precede or follow the myopathy. Typical signs are a heliotrophic rash, oedema of the eyelids, mechanic's hands, Gottron papules at extensor surfaces and subcutaneous calcification. Myalgia is not typical, but can occur. Patients with a severe course of DM can develop dysphagia and dysarthria. Other important complications are the detection of interstitial lung disease (ILD) [4] or tumour [5].

Clinically amyopathic DM (CADM) is a subtype in which patients present with typical skin changes and without or only minimal signs of a myopathy [6]. It makes up to 20% of all patients with DM and can also be associated with ILD [7]. For the anti-CADM-140 antibody, a correlation between DM/CADM and the prediction of outcome of a rapid progressive ILD has been described [4].

The pathology of DM includes binding of immune complexes to endothelium cells with subsequent activation of the complement system and cell lysis, mediated by the membrane-attack complex (MAC) [8]. This leads to necrosis of these cells, and a reduced number of capillaries in the muscle can be seen [9]. The blood supply becomes insufficient, which is believed to cause perifascicular atrophy.

This classical concept has been challenged recently, in that Greenberg's group [10] reported a type I interferon (IFN)-mediated cascade and suggest that this is a predominant element of the pathology. The type I IFN-(α/β)-induced genes are overexpressed in muscle, skin and blood and correlate significantly with the disease activity [11]. Dendritic cells are suggested as antigen-presenting cells and are a potential source of IFNs [10]. It is so far unclear as to which of these cascades precedes or is predominant.

Within the inflammatory tissue, there is an overexpression of proinflammatory mediators, including transforming growth factor (TGF)-β, major histocompatibility complex (MHC)-I, IL-1β, CCL-3, CCL-4, etc. [12–14]. The extravasation of immune cells to the muscle tissue is enhanced by up-regulation of the vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 on endothelial cells and binding to their receptors very late antigen (VLA)-4 and lymphocyte function-associated antigen (LFA)-1 on immune cells [15]. As cellular components of the immune system, T cells, B cells, macrophages and plasmacytoid dendritic cells are found in perimysial and perivascular areas.

In the skin, typical findings are a vacuolar degeneration of epidermal basal cells with epidermal atrophy and dermatitis with lymphocytes and macrophages [16,17]. Depositions of MAC are found along the dermo–epidermal junction and along the vessels [18].

Polymyositis (PM)

The clinical symptoms of PM include a muscular weakness of proximal muscles, mainly with a subacute onset and marked elevation of the CK [9]. The weakness is usually most severe in the pelvic girdle and shoulders. The neck flexors are commonly affected, and in some patients also the neck extensors [19].

The age- and gender-adjusted incidence is 3·8 and the prevalence in the United States is 9·7 per 100 000 people [1]. In the opinion of the authors and other experts, PM is overdiagnosed, and not all studies have been based upon a diagnostic muscle biopsy.

A biopsy is indispensable to distinguish PM from other myopathies. Cellular infiltrates are composed of macrophages and cytotoxic $CD8^+$ T cells [9]. These cells can surround or even invade non-necrotic fibres, a feature which is not usually observed in DM.

The pathogenesis is characterized by local activation of immune cells in skeletal muscle. The proinflammatory milieu includes expression of cytokines such as IFN-γ, IL-6, IL-1β, tumour necrosis factor (TNF)-α and TGF-β [12,20], as well as chemokines such as IL-8, CCL-2, CCL-3, CCL-4, CCL-5, CXCL-9 and CXCL-10, contributing to the local inflammation, and are the attracting stimulus for immune cells [14]. An efficient extravasation of immune cells is mediated by anchoring receptors on immune cells (e.g. VLA-4, LFA-1) and their binding to adhesion molecules, which are up-regulated on endothelial cells (e.g. ICAM-1 and VCAM-1). Extracellular matrix proteins can be degraded by metalloproteinases 2 and 9, which were identified in PM and can contribute to the migration of T cells [21]. These enzymes are induced by cytokines and secreted by inflammatory cells. MHC-I, which is up-regulated ubiquitously by muscle fibres under proinflammatory conditions, seems to be pivotal for the interaction of muscle fibres and immune cells [22,23].

Necrotizing myopathy (NM)

The clinical presentation of NM, recently also termed immune-mediated necrotizing myopathy or necrotizing autoimmune myopathy, includes a progressive, symmetrical weakness of the proximal muscles of arms and legs. Clinically, NM is indistinguishable from PM. Myalgia can occur in up to 80% [24]. In severe cases, dysphagia and dysarthria can develop [25,26].

This group of NM is heterogeneous and includes autoimmune inflammatory mechanisms, paraneoplastic conditions, exposure to toxins or drugs as well as combinations of these mechanisms [27]. Myositis-specific autoantibodies against single recognition particle (SRP) [28] or 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMGCR) [29] can be detected in a subset of 4–6% of patients with myositis and ~60% of patients with NM [29,30]. Our knowledge about the epidemiology is scarce. In studies with small cohorts, a male preponderance of 61% was found [24]. The mean age at onset for SRP-associated NM is in the 5th decade [25,26] and for HMGCR-associated NM in the 6th decade [26,29].

A biopsy is required to make the diagnosis. The major findings are scattered necrotic muscle fibres [31,32]. Sparse inflammatory cells may surround the necrosis. Macrophages are predominant and few lymphocytes are present, which were identified as $CD4^+$ and $CD8^+$ T cells [27]. The interaction of these cells is hypothesized to play an important role in the progression and pathogenesis of NM, but the major part of the pathogenesis is still unknown. The expression of MHC-I in necrotic or regenerating fibres appears to be non-specific.

Most patients with SRP autoantibodies fulfil the criteria for NM; the diagnosis of PM is made only in few patients [30]. It is well known that statins and fibrates can lead to toxic myopathy and the risk increases with the daily dosage of the statin [33]. Two-thirds of myositis patients with HMGCR autoantibodies have previously been exposed to statins [29].

Inclusion body myositis (IBM)

IBM is considered to be the most frequently acquired myopathy after the 50th year of life. The prevalence in Australia per million people was found to be 9·3 in the general population and 51·3 in people aged over 50 years [34]. In contrast to PM and DM, there is a male preponderance [35,36].

IBM develops slowly, progressively and painlessly over years, leading to a mainly asymmetric paresis [35,36]. The flexion of hand and fingers and knee extension are typically affected. The development of dysphagia is typical for IBM, and at least minor swallowing difficulties are observed in 65–80% of the patients [37]. Dysphagia can precede the weakness in arms and legs. Ambulation of the patient is often impaired and assisting devices are commonly required during the course of the disease. The time from disease onset until the first use of a wheelchair ranges from 14 to 16 years [35,36]. After a median time of 24 years, patients are completely wheelchair-dependent [35]. Although the disease progresses slowly and leads to major disabilities, the patient's life expectancy is normal [35].

The diagnostic criteria proposed by Griggs *et al.* [38] rely very much on the histopathology. The criteria of the European Neuromuscular Centre (ENMC) define a definite or possible IBM by histological as well as several detailed clinical features [39,40].

Muscle biopsy reveals inflammatory and degenerative mechanisms. The inflammatory process is similar to PM, with an invasion of non-necrotic fibres by macrophages and cytotoxic $CD8^+$ T cells [15]. There is an over-expression of metalloproteinaeses 2 and 9 on non-necrotic muscle fibres, as in PM [21]. The pattern of expression of chemokines and cytokines is also comparable or even higher than in PM [12]. Degenerative components include rimmed vacuoles and intracellular deposits of β-amyloid which are visualized, for example, by histochemical staining with Congo red [41] or thioflavine-S [12]. Other neurodegeneration-related proteins accumulate similarly, including p-tau, presenilin 1, apolipoprotein, γ-tubulin, clusterin, α-synuclein and gelsolin [41]. Cell stress appears to be a crucial component of the complex pathogenesis of IBM, as evidenced by co-localization of αB-crystallin and APP/β-amyloid [42]. It has been suggested that, under proinflammatory conditions, inducible nitric oxide synthase is up-regulated and causes fibre death [43]. Macroautophagic processing has been attributed to contribute to the accumulation of aberrant proteins [44], particularly under proinflammatory conditions [45,46].

Focal myositis and overlap syndromes

Focal forms of myositis involve only one or few distinct muscles of one arm, leg or eye [47]. The causes of focal myositis include sarcoidosis, systemic lupus erythematosus, Crohn's disease or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Oral therapy with corticosteroids can be effective, but chronic forms may require immunosuppression or even local radiotherapy for ocular myositis.

Overlap syndromes are defined as a combination of DM/PM, rheumatoid arthritis, scleroderma, systemic lupus erythematosus or Sjögren's syndrome [48]. It is also hypothesized that overlap syndromes are defined clinical entities, and more than simply a combination of two diseases. This hypothesis is based on the finding of specific autoantibodies in some cases, e.g. in anti-synthetase syndromes. Extramuscular symptoms such as arthritis and Raynaud's phenomenon are most common [49]. Laboratory, electromyographic and muscle biopsy findings are similar to other forms of myositis. Overlap syndromes are associated with autoantibodies such as Jo-1, PM/SCL, U1RNP and others [50]. Patients are treated with corticosteroids, immunosuppressants or monoclonal antibodies, such as anti-TNF-α or anti-CD20 [48].

Myositis-specific autoantibodies (MSA) and associated diseases

MSA can be found in patients with myositis and support the correct diagnosis. Most common among these is the Jo-1 autoantibody, which is found in approximately 20% of adult patients with myositis [51,52]. It belongs to the group of aminoacyl-tRNA-synthetase autoantibodies and targets histidyl-tRNA-synthetase. Other autoantibodies, including PL-7, PL-12, OJ, EJ, KS, Ha and Zo, are directed against different synthetases and their frequency is below 5%. They lead to a similar phenotype, called anti-synthetase syndrome. Clinical manifestations are ILD, myositis, arthritis, fever, etc. With a frequency of 79–95%, ILD is the most common extramuscular manifestation [53]. The above-mentioned anti-CADM-140 also shows a strong association to ILD [4].

It has been well established that the Mi-2 autoantibody is a marker for DM, associated with the classical cutaneous phenotype without ILD or malignancy [54]. Some newly described autoantibodies are under further investigation, and evidence shows that MDA5, NXP2 and transcription intermediary factor (TIF)-1γ are also associated preferentially with DM [55,56]. The anti-155/140 autoantibody targets the TIF-1γ [55] and is associated strongly with malignancy [54], which should prompt thorough tumour screening in these patients.

Possible IBM-specific autoantibodies were detected in a recent study [57]: in sera of 25 IBM patients, 52% displayed an antibody against a 43 kDa protein while other samples from healthy controls or other diseases did not recognize this protein. Another study revealed the reactivity of recombinant immunoglobulins produced by plasma cells derived from IBM muscle tissue. For one of these recombinant immunoglobulins, desmin was identified as the target [58]. Two recent studies have identified an autoantibody to a muscle protein of 44 kDa ('Mup44'), which was identified as the cytosolic 5'-nucleotidase 1A (cN1A) [59,60]. This antibody is present in ~60% of patients with IBM, but it is not specific in view of other patients with myositis that are also positive. For all antibodies it is important to be aware of the fact that it is still unknown whether or not they are pathogenic or simply an epiphenomenon as the result of promiscuous activation of the immune system.

One recent analysis of epidemiological studies with the total number of 2439 patients revealed an underlying malignoma in up to 24% of DM and 10% of PM patients [5]. This association was found for several tumours, most of all lung tumours in western countries and nasopharyngeal cancer in Asia and northern Africa [5]. Most tumours are detected within the first years after the onset of myositis. This supports the hypothesis that the development of myositis in individual cases might be paraneoplastic [61]. NM has been shown to be associated with gastrointestinal tumours, small cell lung cancer or breast cancer [62]. For IBM, only few cases exist of the co-existence of a malignoma.

Cardiac involvement is observed regularly in patients with DM or PM [63]. Typical findings are electrocardiographic changes, valve disease, coronary vasculitis, ischaemia, heart failure and myocarditis. In patients with myositis, extramuscular manifestations such as rapid-progressive ILD, severe cardiac involvement or tumour can lead to a poor prognosis.

Diagnostics

A precise medical history and medical examination are prerequisites for the accurate diagnosis of myositis. The paresis distribution may reveal a pattern typical for IBM, as opposed to a proximal weakness, which is similar in DM, PM and NM. Laboratory examination usually reveals an increased CK, and sometimes other enzymes such as LDH, AST or ALT and myositis-specific autoantibodies may be detected.

Needle EMG of affected muscles usually displays a myopathic pattern, and signs of acute damage may be noted. A retrospective Dutch study with 98 patients with myositis revealed that none of the patients with the diagnoses DM, PM or IBM had a normal needle EMG [64]. Alterations in signal intensity within the muscle can be detected using MRI [65]. In the early stages of myositis there is oedema; in later stages fatty transformation or muscle atrophy can be observed. Even though these changes are not specific to myositis and can also be seen, e.g. in injuries, muscle infarction, subacute denervation or rhabdomyolysis, they are valuable to identify affected muscle groups and make an adequate diagnosis. Most importantly, MRI may help to identify subclinical involvement of muscles, which may point to another disease such as a muscular dystrophy.

A biopsy is the most important and most invasive step to make the correct diagnosis; it is the only way to distinguish between the different subtypes of myositis. It is crucial to rule out muscular dystrophy or other forms of a hereditary myopathy. To achieve this, it is important to choose a representative muscle for the biopsy: usually, this muscle should demonstrate moderate paresis. MRI can help to identify end-stage changes of tissue destruction.

A chest X-ray should be performed for the detection of an ILD. High-resolution CT may be performed, particularly in patients with anti-synthetase autoantibodies and anti-CADM. This technique allows the detection of pulmonary changes prior to the appearance of clinical symptoms [66]. In patients with high risk of a cardiac involvement, regular cardiological examinations should take place. Assessment of the bone density should be considered during prednisone therapy at a daily dosage of more than 5 mg [67].

While dysphagia is reported to be highly frequent in IBM, patients with DM and PM also often display signs of swallowing difficulties [37,68]. A high incidence of self-reported dysphagia in patients with myositis was found, suggesting that every examination should include questions regarding this topic [69]. When dysphagia is reported, additional diagnostics may be conducted, including videofluoroscopy or flexible endoscopic evaluation of swallowing (FEES) [70].

Treatment of DM, PM and NM

Treatment is usually initiated with pulsed intravenous glucocorticosteroids, e.g. 250–1000 mg prednisolone per day for 3–5 days (Fig. 1). The following standard oral treatment usually consists of prednisone 1 mg/kg/day. This dosage is usually administered for at least 4 weeks. After initial stabilization, which may take 4–12 weeks, the dose can be tapered every 1 or 2 weeks by 10 mg until 20 mg/day is reached. Subsequently, the taper is slowed to a reduction

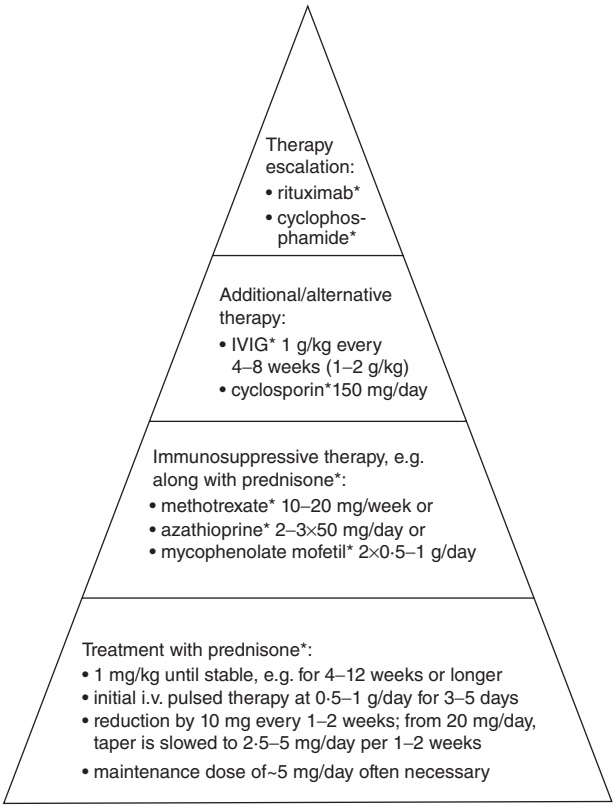

Fig. 1. Therapy of dermatomyositis, polymyositis and necrotizing myopathy. The dose is to be adapted in each individual case; further information within the text. Adapted from [109] with the kind permission of Springer Science and Business Media.

by 5 mg until 10 mg daily and to 2·5 mg thereafter. The therapy is based on early reports suggesting a positive effect of corticosteroids on muscle strength [71], even though this effect has never been proved formally in a prospective double-blind study; nor has a scheme for the tapering ever been proved. The rate of reduction is dependent upon the patient's response, and in the case of renewed deterioration the taper has to be stopped or slowed or the dosage even increased. An alternate day regimen is a useful alternative and may help to reduce side-effects. Monthly 4-day courses of 40 mg dexamethasone as an 'oral pulse therapy' displayed comparable efficacy to daily prednisone, but significantly fewer side effects [72]. The risk of a fracture is increased under therapy with prednisone in a daily dosage of more than 5 mg or by duration of more than 3 months. Concomitant treatment with 1000 mg calcium carbonate and 500 IU vitamin D per day is advisable [67]. Steroid-induced myopathy is an important side effect of glucocorticosteroids, with slowly progressive proximal muscle weakness that can mimic a relapse [73]. Acute changes in EMG are typically expected in a relapse and may help to distinguish one from the other.

Additional immunosuppressive therapy can be started simultaneously, unless only very mild symptoms are present. This treatment usually helps to spare prednisone. A recent Cochrane Review reveals the lack of randomized controlled trials (RCT) concerning immunosuppressive therapy in myositis [74]. Only 10 studies with a total of 258 patients were considered relevant and included. Six studies compared the therapy with immunoglobulin (IVIG), etanercept, eculizumab, infliximab, azathioprine or leucapheresis with placebo, and significant improvement in muscle strength was detected only for IVIG. The other four studies compared the effect of two immunosuppressive therapies and no statistically significant difference was found. It can be summarized that there is no convincing evidence for the efficacy of the commonly used immunosuppressive agents in myositis such as methotrexate (MTX), azathioprine and mycophenolate mofetil (MMF). However, in view of the immunopathogenesis, an international consensus of experts has recommended that immunosuppressants should be used. More prospective and controlled studies with an adequate cohort size are necessary.

MTX is administered in a weekly single dose of 5–20 mg, usually 10–15 mg, followed by leucoverin rescue on the subsequent day. The application of high-dose folic acid can reduce the toxicity and side effects of MTX as the drug interferes in the folate metabolism [75]. Common side effects include increase of the liver enzymes. Treatment with azathioprine is started with a daily dosage of 50 mg over 1 week. The dosage is increased weekly and monitored by the number of lymphocytes, which should be 600–1000/μl. A major potential side effect is bone marrow suppression, especially in patients with thiopurine methyltransferase deficiency. Thus, the activity of this enzyme should be measured before initiation of the treatment. A further frequent side effect is an increase of the liver enzymes. Frequent controls of the blood count and liver enzymes are essential during treatment with an immunosuppressant. The interval can be extended once the maintenance dosage is reached. MMF is the third common and orally administered immunopressant in myositis. Side effects are less frequent compared to MTX or azathioprine and include toxicity on kidney and liver. The therapy is started with a dosage of 500 mg twice daily and can be increased to 2 g or even 3 g per day. The use of cyclosporin as another alternative is limited by its common toxicity on liver and kidney.

IVIG can be tried as an alternative when the side effects from immunosuppressants outweigh their clinical benefit. It can also be used as an add-on treatment during a relapse or when immunosuppressants are not sufficiently effective. In addition, IVIG is a treatment option when immunosuppression is not wanted, e.g. in child-bearing women or adolescent patients. Usually, a total dosage of 2 g/kg is administered initially. The therapy is repeated regularly every 4–8 weeks with a dose of 1 g/kg, and tapering depends upon the treatment effect. Relevant side effects are an increased risk for thrombosis, fever and allergic reactions/anaphylaxia [76]. The risk for the allergic reaction is

increased in patients with an immunoglobulin (Ig)A deficiency, which should be excluded before starting the treatment.

Women of childbearing potential can be treated with IVIG as a safe option [77]. MTX, azathioprin and MMF are potentially teratogenic, which makes an effective contraception essential [78]. A pregnancy should not be planned before withdrawal from immunosuppressants for several months, as active metabolites can persist in the tissues for several weeks [79].

In recent studies, the effect of monoclonal antibodies in the treatment of myositis was investigated: rituximab leads to a depletion of B cells by targeting CD20. A prospective, double-blind trial with rituximab in myositis revealed a steroid-sparing effect and 83% of the patients who were refractory to prior treatments improved during a period of 44 weeks [80]. Similar results were found in smaller cohorts [81,82]. The TNF-α inhibitor etanercept was tested in a small, double-blind, placebo-controlled study including 16 patients with DM [83]. Even though the patients experienced no improvement, a significant steroid-sparing effect was detected.

Other substances, such as cyclosporin or cyclophosphamide, are used less often, due partly to a higher risk of side effects. However, these drugs can be very useful for escalation therapy in individual patients, particularly when all other treatments have failed.

Based on our clinical experience, we treat our patients with 1 mg/kg oral prednisone daily. Upon improvement, e.g. after 6–8 weeks, we slowly taper the prednisone and start with azathioprin at 50–150 mg/day. We consider MMF and MTX as second or third choices, e.g. in the case of side effects from azathioprin. If treatment with any of these drugs alone remains ineffective, we additionally administer intravenous immunoglobulins. Options for treatment escalation include a CD20 blockade with rituximab or maximal immunosuppression with cyclophosphamide. We recommend regular physiotherapy, e.g. twice a week, as an essential part of the treatment. There is growing evidence for the safety and beneficial effects of physiotherapy and home exercise programmes in myositis [84].

Treatment of IBM

Treatment of IBM is a challenge, despite increasing understanding of its pathology. It remains controversial whether or not the inflammatory mechanisms are cause or consequence of the degeneration or if both cascades occur independently. An underlying degenerative cascade could explain the resistance of IBM to immunosuppression. Prednisone, the standard therapy of the other subtypes of myositis, is usually not effective in IBM [85]; however, individual patients may experience at least a temporary improvement. Conversely, one recent study revealed that progression towards handicap for walking was more rapid among patients receiving immunosuppressive drugs [36]. This finding could be explained by either a side effect of the treatment or the suggestion that more severely affected patients receive treatment more often.

Other studies with MTX, compared to MTX and anti-T lymphocyte globulin [86], etanercept [87], oxandrolone [88] or normal or high-dose IFN-β [89,90], failed to identify clinical efficacy. MTX compared to placebo led to a significant decrease of the CK but the disease progression was unaltered [91]. More encouraging is a proof-of-principle study in which alemtuzumab seemed to reduce the disease progression for up to 6 months, and in some patients the muscle strength was improved [92]. However, these data should be interpreted with care, as this was an unblinded study and the rate of the yearly disease progression was higher compared to recent natural history studies [35,36]. Major side effects of alemtuzumab are the development of an autoimmune thyroiditis or idiopathic thrombocytopenic purpura [92]. In three controlled prospective studies with IVIG, no increase of the limb strength could be observed [93–96], whereas the dysphagia was improved significantly [94,97,98].

Most recently, pilot trials with other drugs have been performed. Simvastatin is supposed to have anti-inflammatory effects, but it failed to improve muscle weakness after 12 months of treatment [99]. Two other trials in IBM have been completed: lithium, an inhibitor of the tau-phosphorylating enzyme glycogen synthase kinase-3β, and arimoclomol, a drug that reduces the heat shock response and has been studied in amyotrophic lateral sclerosis [100] [NCT00917956 (http://www.clinicaltrials.gov/ct2/show/NCT00917956); NCT00769860 (http://www.clinicaltrials.gov/ct2/show/NCT00769860)]. Further treatment studies on IBM include BYM338/bimagrumab and follistatin gene transfer and are currently ongoing [NCT01925209 (http://www.clinicaltrials.gov/ct2/show/NCT01925209); NCT01519349 (http://www.clinicaltrials.gov/ct2/show/NCT01519349)].

In a small open study, a statistically significant improvement of the most affected muscle groups in IBM was shown by a 16-week twice-a-day home exercise programme [84]. In view of the resistance of IBM to immunosuppressive therapy, we consider physiotherapy and regular home exercise to be an essential element of the therapy.

Treatment of dysphagia

As noted previously, dysphagia can occur in all subtypes of myositis. A high percentage of patients with IBM is affected [35–37]. Dysphagia leads to a reduced quality of life and the risk for malnutrition and aspiration pneumonia is increased [101]. Treatment with IVIG improves swallowing in IBM (see above). IVIG is also beneficial for patients with prednisolone-resistant dysphagia and DM or PM. In one study, approximately 82% of 73 patients were able to return to oral feeding [102].

Other uncontrolled studies, each with a small number of patients, addressed the effect of the following interventions in IBM: cricopharyngeal myotomy, pharyngoesophageal dilatation, percutaneous endoscopic gastrostomy (PEG) and injection of botulinum toxin. A benefit was shown for both myotomy and dilatation, but the results were limited by the number of only 10 patients [98,103,104]. So far, treatment with botulinum toxin has shown different results, ranging between no effect and improvement in swallowing for several months [104,105]. Among the causes of death in patients with IBM, cachexia and (aspiration) pneumonia are increased significantly in comparison to the normal population [35,36]. PEG may be helpful as prevention, but further studies regarding this point are missing. In one retrospective study, five of six patients with PEG died because of aspiration and respiratory failure, while the cause of death of the sixth patient remains unknown. This finding could be explained by the fact that patients with severe dysphagia and PEG still exhibit an increased risk for aspiration pneumonia [106]. Similar to IBM, a balloon dilatation might be beneficial in PM and improve swallowing [107].

In summary, IVIG might be useful in patients with severe swallowing disturbances. The literature concerning the benefit of invasive interventions is controversial and, at present, no procedure can be recommended. A recent study concerning the underlying mechanisms of dysphagia in myositis revealed that an abnormal hyolaryngeal excursion is more likely to be the reason than the often-supposed failed relaxation of the upper oesophageal sphincter [108]. The authors would like to point out that the often-performed myotomy is not indicated in patients with normal relaxation. Controlled trials are much needed to address the treatment of dysphagia, particularly in IBM.

Conclusions

The four different forms of myositis (DM, PM, NM, IBM) can be distinguished by certain clinical clues on examination and additional diagnostics, particularly a muscle biopsy. Despite many recent studies and growing knowledge of the pathogenesis of myositis, our treatment of DM, PM and NM is still based more on experience than on prospective double-blind studies with an adequate number of patients. IBM remains a challenge due to its complex pathogenesis and lack of effective treatment. In view of the growing interest in rare disorders and the development of new therapeutic approaches, including novel biologicals, hope for better care of these patients appears to be justified.

Disclosures

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