Netherlands
The Journal of Medicine

REVIEW

Dermatomyositis and polymyositis: new treatment targets on the horizon

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ABSTRACT

Polymyositis (PM) and dermatomyositis (DM) are rare idiopathic inflammatory myopathies (IIM) with a presumed autoimmune pathogenesis. Typical features are subacute onset, proximal, symmetric muscle weakness, elevated serum creatine kinase, and mononuclear cell infiltrates in the muscle biopsy. Strong support for an autoimmune pathogenesis comes from histopathological findings in biopsies of affected muscles. Furthermore, the association with autoantibodies supports the notion that immune-mediated inflammation is involved. PM and DM may occur in isolation or in connection with a connective tissue disease or cancer. The current treatment for IIM consists of first-line high-dose steroids and various conventional second-line treatments. Improvements in treatment for IIM are hampered by difficulties in the design of trials and the low incidence and prevalence of the disease. Cytokines and chemokines are factors involved in the inflammatory process in IIM, and are candidates for future therapeutic targets. Preliminary data with anti-tumour necrosis factor therapy are not very promising, but results of blockers of the lymphotoxin signalling pathway are to be awaited. Anti-B cell therapy may be a valuable therapeutic option for treatment of refractory IIM. The effects of anti-interferon-alpha in IIM are to be awaited, as are results of other anti-cytokine therapies and anti-chemokine therapy. Outcome measures to be used in clinical trials in IIM include at present the core sets of outcome proposed by the International Myositis Assessment Clinical Study Group (IMACS).

KEYWORDS

Polymyositis, dermatomyositis, idiopathic inflammatory myopathies, immunopathology, therapeutic prospects

INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies (IIM) with a presumed autoimmune pathogenesis. Typical features are subacute onset, proximal, symmetric muscle weakness and mononuclear cell infiltrates in the muscle biopsy.[1] PM and DM occur in isolation, or in connection with a connective tissue disease (CTD) or cancer.[2,3] High-dose prednisone is the treatment of choice on an empirical basis; its effect has not been investigated in a randomised controlled trial (RCT). DM and PM often give rise to severe chronic disability and may be complicated by life-threatening impairment of swallowing and respiratory function.[2] Sporadic inclusion-body myositis (sIBM), also considered to be an idiopathic inflammatory myopathy and a common myopathy in middle age and older adults,[4] is addressed to outline its distinguishing features in the differential diagnosis of IIM.

CLASSIFICATION AND DEFINITION

PM and DM were already described in the 19th century.[5] However, it took nearly a century before diagnostic criteria for DM and PM were proposed based on clinical features (subacute, symmetrical proximal weakness, and typical skin abnormalities for DM) and ancillary investigations. The latter included muscle biopsy abnormalities (necrosis, regeneration, perifascicular atrophy, inflammatory exudates), elevated serum creatine kinase (sCK) and electromyographic changes (short duration, low-voltage motor unit action potentials, and spontaneous activity).[6] These criteria were initially developed for research purposes. The usefulness of this Bohan and Peter classification was challenged when new diagnostic modalities such as myositis-specific antibodies became

available.[7] In addition, sIBM, although already described in 1971,[8] was not recognised as a distinct disease entity at the time, and therefore probably misdiagnosed as PM, and the same holds true for muscular dystrophies in which cellular infiltrates may be prominent, such as dysferlinopathy and facioscapulohumeral dystrophy.[9,10] In 1984, Arahata and Engel[11] and subsequently Dalakas[12] suggested another classification including sIBM. This was based on histopathological and immunohistochemical findings of muscle tissue suggesting that the immune mechanism in DM is humoral and targets the intramuscular microvasculature, whereas PM and sIBM are characterised by an antigen-directed cytotoxic T cell attack on myofibres expressing class 1 major histocompatibility complex antigens. Recently, at a consensus workshop under the auspices of the European Neuromuscular Centre (ENMC) a new classification was proposed.[13] The main differences from previous classifications included the paradigm shift with regard to the prevalence of polymyositis, which appeared to be considerably less frequent in several parts of the world[3,14] and the recognition of two immune-mediated disease entities: necrotising myopathy and non-specific or overlap myositis.[3,15,16] In the ENMC classification non-specific myositis is defined by subacute onset, progressive proximal weakness, elevated sCK, perivascular, perimysial inflammatory cell infiltrate or scattered endomysial CD8+ T cells that do not clearly surround or invade muscle fibres. In a Dutch retrospective study,[14] non-specific myositis was found in 39% of the patients with a previous diagnosis of myositis, with subacute onset of symmetric, proximal weakness excluding other neuromuscular disorders and 40% of these patients developed a connective tissue disorder. In a French-Canadian study,[3] 67% of the IIM patients were diagnosed as overlap myositis on the basis of clinical features and the presence of autoantibodies. Immune-mediated necrotising myopathy is defined by subacute or insidious onset, progressive symmetrical weakness of the proximal muscles associated with an elevated sCK, and many necrotic muscle fibres as the predominant abnormal histological feature. Inflammatory cells are sparse and perivascularly located or even absent.[13] Immune-mediated necrotising myopathy was found in 19% of the Dutch patients with IIM.[14] Patients with immune-mediated necrotising myopathies were found to have a strong association with antibodies directed against the signal recognition particle (SRP). Recently, a unique subset of patients with anti-200/100 kd autoantibodies was reported in whom prior statin use was a frequent observation.[17] The recognition of non-specific or overlap myositis and immune-mediated necrotising myopathy caused a shift of the prevalence of polymyositis. Some authors found this disease in only 2% and 9% of the patients with IIM, respectively,[3,14] whereas in other populations PM appeared to be rather common.[18] There is also some controversy about the clinical profile of polymyositis. Amongst the group of Dutch patients designated as PM on the basis of histopathological findings, it was noticed that a proportion developed progressive muscle weakness despite immunosuppressive treatment and ultimately showed a clinical picture consistent with sIBM. Although the muscle biopsy lacked rimmed vacuoles, a microscopic entity considered to be specific for sIBM,[14] these patients were no longer considered to have PM, but designated as having sIBM. Others recognised a new category of IIM, i.e. PM/IBM characterised by clinical features of sIBM but with muscle biopsies that lacked rimed vacuoles, the canonical feature of sIBM.[18]

DIAGNOSIS OF MYOSITIS SUBTYPES

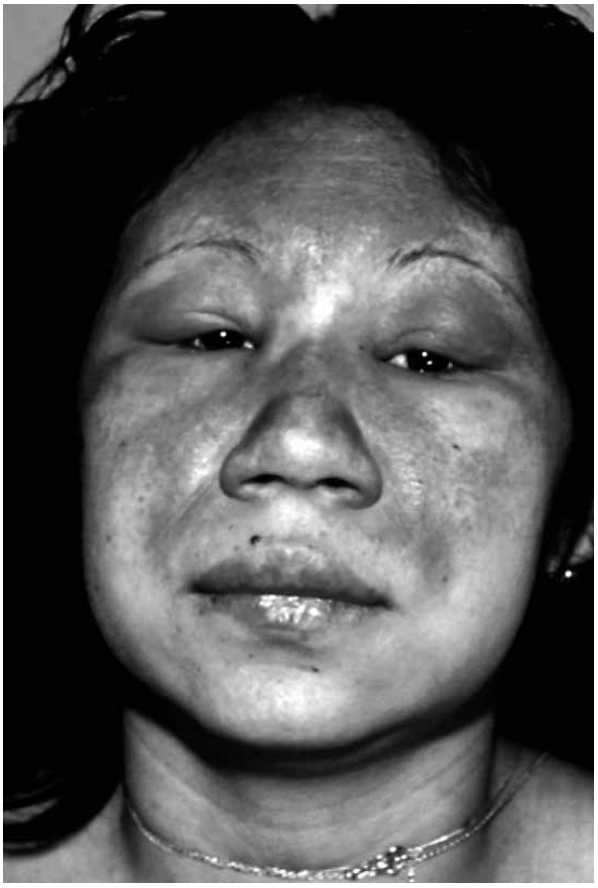
Clinical picture

PM is characterised by progressive, symmetric, proximal muscle weakness. Neck flexor weakness and dysphagia are observed in a fair proportion of the patients. A study assessing the distribution and severity of muscle weakness in DM and PM showed a greater severity of proximal weakness in PM in comparison with DM. The five weakest muscle groups were the hip flexors, hip extensors, hip abductors, neck flexors and shoulder abductors.[19] Interstitial lung fibrosis is a common complication especially in patients who have anti-synthetase antibodies. DM is identified by a characteristic rash accompanying or preceding muscle weakness. The skin manifestations include a heliotropic rash (blue-purple discoloration) on the upper eyelids in many cases associated with oedema (sensitivity 67% and specificity 99.6%) (*figure 1*), Gottron papules (symmetric, livid papules on the dorsal side of interphalangeal and/or metacarpophalangeal joints, on the dorsal side of elbows, knees or medial malleoli, sensitivity 62% and specificity 98.7%),[20] Gottron sign (symmetric erythematous or livid atrophic maculae with or without oedema on elbows, knees and medial malleoli), and an erythematous rash on the face, neck and anterior chest (V sign) or back and shoulders (shawl sign).

Biochemistry

In adult DM, sCK is slightly to moderately (2-10 x the upper limit of normal) elevated in 20 to 90% of the patients.[6,21] Patients with muscle weakness more often have an elevated sCK than those with amyopathic DM. Generally speaking, there is no relationship between the sCK activity at onset of the disease and outcome. However, in the individual patient who has been in remission, a rise in sCK activity may herald a relapse. There is uncertainty about the sCK activity in PM since the published articles

Figure 1. *Heliotrope erythema of the face (characteristic feature of dermatomyositis)*



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are probably contaminated with sIBM cases. In sIBM, sCK is slightly (<5x the upper limit of normal) elevated in 90% of the cases and in only 7% is it ≥10x elevated.[22,23] Of note, an inflammatory myopathy with perimysial pathology amenable to steroid treatment was recently reported, which was characterised by high aldolase activity while sCK was normal.[24] This observation remains to be confirmed by other groups. Erythrocyte sedimentation rate is usually normal or only mildly elevated in IIM and is not a reliable indicator of disease severity.

Electromyography

Only uncontrolled research on the usefulness of electromyography (EMG) for the diagnosis of IIM has been published and studies on groups of patients with PM have not been performed. Short-duration, low-voltage polyphasic motor unit action potentials were observed in nearly 100% of the patients with DM, PM and sIBM, whereas fibrillations and short-wave activity were found in three-quarters of the patients.[25] Spontaneous muscle fibre activity occurred in 80 to 100% of the cases. Therefore, it seems justified to consider EMG as an adjunct to the clinical, biochemical and histopathological investigations, although the findings are non-specific and do not distinguish between the various subtypes of IIM. EMG has no added value in cases of DM with characteristic skin changes. EMG can be helpful to distinguish between a relapse of DM or PM and steroid myopathy, since spontaneous muscle fibre activity is not found in steroid myopathy.[26]

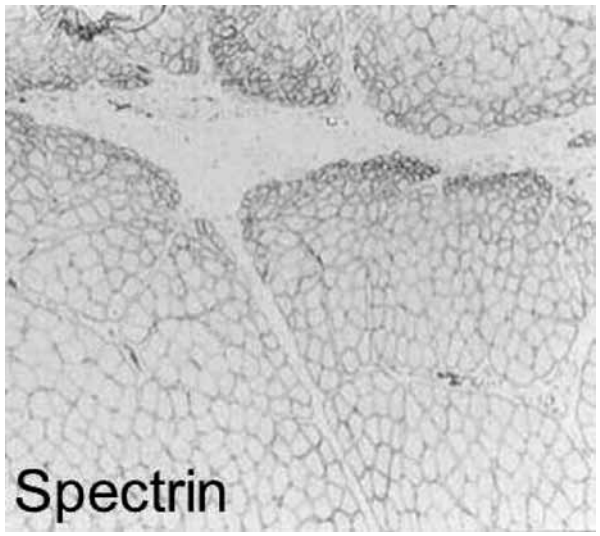
Muscle imaging

Muscle imaging is a promising diagnostic tool in IIM. MRI can demonstrate muscular oedema by showing areas of high signal intensity on STIR (short tau inversion recovery) and fat-suppressed T2-weighted sequences, even in clinically asymptomatic muscles.[27] Recommendations to perform an MRI as a guidance for the muscle biopsy are based on relatively small prospective studies and on studies including only patients with an established diagnosis of IIM.[28,29]

Histopathology

The predominant histological features in PM are variability in fibre size, scattered necrotic and regenerating fibres, and perivascular and endomysial inflammatory cell infiltrates consisting mainly of CD8+ T cells and macrophages. These inflammatory cells surround and sometimes invade apparently non-necrotic muscle fibres expressing major histocompatibility class 1 antigens.[11,30,31] Since invasion of non-necrotic muscle fibres is actually not very common in myositis patients, from a pragmatic point of view, this feature should not be required for the clinical diagnosis of PM, and perivascular, perimysial or endomysial inflammation without actual invasion of non-necrotic muscle fibres may suffice for a diagnosis of PM in the proper clinical context.[32] A highly characteristic microscopic feature of DM is perifascicular atrophy (*figure 2*), which is caused by the degeneration of muscle fibres at the periphery of the fascicles, although this is a late finding and is found in perhaps only 50% of adult cases when biopsied early in the course of their illness. Quantitative morphological analysis suggests that focal capillary depletion is one of the earliest changes in DM.[33] Immunofluorescence studies revealed the deposition of the components of the complement system (complement-membrane complex) in or around microvascular endothelium in a significant proportion of capillaries.[34] These observations support the concept that an immune complex- or antibody-mediated response against a vascular-endothelial component is a primary pathogenetic mechanism in DM.[1] Inflammatory infiltrates are composed primarily of macrophages, B cells and CD4+ cells in the perivascular and perimysial regions.[11,30] These CD4+

Figure 2. *Spectrin frozen muscle biopsy section shows perifascicular atrophy in dermatomyositis. Fascicles in this sample show atrophy, predominantly at the periphery, along the connective-tissue border. Ischaemia or chronic overexpression of type 1 interferon by dendritic cells in the perivascular and perimysial regions, which may be toxic to nearby capillaries and the nearby perifascicular muscle fibres, are considered to cause perifascicular atrophy. This finding is characteristic of dermatomyositis, mostly associated with the juvenile form but it is also observed in the adult form*



cells also include significant numbers of plasmacytoid dendritic cells as opposed to T helper cells secondary to microvascular damage. Muscle fibres overexpress type 1 interferon (IFN)-inducible genes and proteins, particularly in the perifascicular regions, even before the development of perifascicular atrophy.[35,36] Of note, increased expression of type 1 IFN-inducible genes is also evident in peripheral blood and levels appear to correlate with disease activity.[37] These observations have led to yet another hypothesis that DM may be caused by overexpression of type 1 IFN by dendritic cells in the perivascular and perimysial regions and this may be toxic to nearby capillaries and the nearby perifascicular muscle fibres. Muscle biopsy is normal or shows non-specific findings in approximately 10 to 20% of the patients, even in those with clinically active disease.[25,38-40] False-negative findings may be due to sampling error caused by the scattered distribution of cell infiltrates, even if clinically affected muscles are chosen as biopsy sites.

EPIDEMIOLOGY

IIM are rare disorders. Most epidemiological data are not accurate since they are based on the diagnostic criteria of Bohan and Peter[6] (see above). In the literature, data are found on the incidence of inflammatory myopathies as a whole (DM, PM and sIBM) which is estimated to be between 5.5 and 7.7 per million person-years, not including those overlapping with CTD (see below).[41-43] Using Quebec physician billing and hospitalisation databases, the prevalence of PM and DM was estimated to be 21.5/100,000 (95% confidence interval (CI) 19.4 to 23.9) in 2003.[44] In children, DM is the most frequent inflammatory myopathy, with an incidence of 1.5 up to 4 x 10^{-6} children per year, and occurring at least two times as often among white girls than boys.[45-47] There are no good epidemiological data on the occurrence of adult DM. The relative prevalence of DM (in comparison with PM together with sIBM) is higher in areas closer to the equator. Genetic risk factors may be involved, although these differ in separate ethnographic populations.[48,49] Given the fact that PM is not strictly defined, epidemiological data on PM are lacking as well.

COMORBIDITY

PM and DM occur isolated or in connection with a CTD or with cancer.[2,3] After the onset of PM, patients have a chance of about one in four to be diagnosed with an associated CTD such as scleroderma, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis and mixed CTD.[2] In a Dutch study, the cumulative risk of incident CTD was highest in subjects with non-specific myositis (clinical PM) and 33% at seven years.[2] Depending on the classification criteria used, the frequency of myositis associated with CTD was 24 to 60% in an analysis of 100 French Canadian patients.[3] The risk of several forms of cancer for adult patients with DM is increased, with a standardised incidence rate of 4.3 (95% CI 2.3 to 8.1), especially during the first three years after the diagnosis of DM is made.[50] However, after five years an increased risk can still be detected.[50] In a Scandinavian study, the risk of cancer was found to be increased before the diagnosis of DM was made (4.5 years (95% CI 2.8 to 8.7). In 71% of patients this occurred in a period less than two years before the diagnosis of DM.[51] A French study found a cumulative incidence rate of malignancy of 21±4% and 28±5% one and five years after the diagnosis of DM, respectively.[52] Cancer is not restricted to DM, but also occurs in patients with PM.[2,50] However, accurate data are lacking due to the ill-defined entity of PM. In cases of immune-mediated necrotising myopathy a high rate of malignancy has been reported.[15]

PM and DM are serious diseases with a disease-related mortality of at least 10%. Mortality is mostly related to cancer, especially during the first years after onset of myositis. Furthermore, in the long term, myositis has a

chronic continuous or polycyclic disease course with major effects on perceived disability and quality of life, despite regained muscle strength.[2]

AUTOANTIBODIES

Detection of autoantibodies may be helpful in the differential diagnosis from other, non-autoimmune myopathies, and they are found in approximately 70% of the patients with PM or DM,[53,54] as recently reviewed.[55] These antibodies are classically divided into myositis-associated autoantibodies (MAAs), which can also be found in subjects with other CTDs, and myositis-specific autoantibodies (MSAs), which are primarily found in subjects with IIM.[56]

Autoantibodies against the histidyl-tRNA-synthetase (Jo-1) are the most common MSAs.[57] They identify a group of patients with a unique clinical syndrome including myositis, interstitial lung disease (ILD), non-erosive arthritis, fever, and characteristic hyperkeratotic lesions along the radial and palmar aspects of the fingers known as 'mechanic's hands'.[58,59] This constellation of symptoms has come to be known as the anti-synthetase syndrome. The presence of Jo-1 antibodies virtually excludes inclusion body myositis.[60] Since the detection of Jo-1 antibodies, a number of additional aminoacyl-tRNA synthetases (ARS) have been identified, including those recognising threonyl-tRNA synthetase (anti-PL-7),[61] alanyl-tRNA synthetase (anti-PL-12),[62] glycyl-tRNA synthetase (anti-EJ),[63] isoleucyl-tRNA synthetase (anti-OJ),[63] asparaginyl-tRNA synthetase (anti-KS),[64] anti-tyrosyl-tRNA synthetase,[65] and, most recently, anti-phenylanalyl synthetase (anti-Zo).[66] Anti-Jo-1 is found in approximately 25 to 30% of myositis patients, and the other anti-ARS autoantibodies occur in 1 to 5% of myositis patients.[67] The various anti-synthetase antibodies seem to be mutually exclusive in that individual patients usually do not produce more than one.[68] The anti-synthetase autoantibodies may be found in patients with either PM or DM, and certain anti-synthetases may be more strongly associated with one or the other disease. However, different studies of the same anti-synthetase yielded very different results.[69] Furthermore, although the relationship between anti-synthetase antibodies and myositis has been studied for almost 30 years, many questions remain about their pathological significance.

Twenty to 30% of DM patients have Mi-2 antibodies, the autoantigen initially recognised as a nuclear protein. Using immunoprecipitation or immunodiffusion, few if any PM patients or normal controls produce Mi-2 autoantibodies.[70-76] As mentioned before, some of the patients with an immune-mediated necrotising myopathy have autoantibodies targeting components of the SRP;[63,77-81] however, the pathological relevance of these autoantibodies remains unclear.[55] As previously mentioned, a novel autoantibody recognising 200-kd and 100-kd proteins was found to be associated with immune-mediated necrotising myopathy in subjects in whom prior statin use was a frequent observation.[17] Novel highly specific MSAs, which are relatively common (13 to 21%) in DM patients and recognise 155-kd and 140-kd proteins, have recently been identified and may be associated with a higher rate of malignancy.[82,83] The identity of the autoantigen recognised by these antibodies has not yet been established.[55] Routine clinical tests for the most recent MSAs are lacking at present, but may prove to be of value in advancing our understanding of the pathogenesis of the diseases and the development of new treatments.

IMMUNOPATHOLOGY

Pathology

In most IIM, except for immune-mediated necrotising myopathy,[84] there is prominent inflammation within the skeletal muscle tissue. However, the tissue constituents toward which the immune responses are directed differ. The primary target of the immune response in DM is the vascular endothelium of perimysial small arterioles and veins and perifascicular arterioles and capillaries. In contrast, the primary targets of the immune response in PM are the muscle fibres themselves. CD8+ cytotoxic T cells surround and invade non-necrotic myofibres, macrophages and CD4+ helper T cells are found in large numbers within the endomysium. Plasmacytoid and myeloid dendritic cells are present in varying amounts within IIM muscle, often associating into nodular aggregates.[85] A complex interregulated network of immunomodulators is involved in the recruitment, diapedesis and migration of these inflammatory cell subsets. Muscle cells actively participate in these immune reactions by expressing major histocompatibility complex I (MHC-I) antigens and costimulatory molecules on their sarcolemma.[86] Blood vessel endothelial cells selectively recruit leucocytes, through upregulation of anchor proteins such as the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1),[87,88] allowing their transmigration from the circulation into the muscle tissue.

Cytokines

Cytokines are soluble chemical messengers that form an integrated signalling network regulating both innate and adaptive immune responses. The primary cellular sources of cytokines are the immune cells, but endothelial cells and muscle fibres can also express these immune regulators. The important role of the catabolic cytokine tumour necrosis factor (TNF) as a

regulator of the chronic inflammation associated with the IIM has previously been established.[89,90] Lymphotoxins (LT), other members of the TNF superfamily, have been implicated in the cytotoxic response of CD8+ T cells towards non-necrotic muscle fibres in PM[91] and are increased in DM patients, where they colocalise to intramuscular follicle-like structures that contain large numbers of T cells, B cells and plasmacytoid dendritic cells.[92] Many other pro-inflammatory cytokines are regulators of inflammatory disease. Interleukin-1 beta (IL-1beta) is significantly upregulated in IIM[93,94] and decreases when patients have been successfully treated with corticosteroids.[95] In patients with DM and PM, serum levels of the related cytokine IL-18 are also increased.[96] Recently, the overexpression of type I IFN in DM and PM has gained attention. Type I IFNs are cytokines expressed from multiple IFN genes and play a critical role in the regulation of the immune system. They appear to be part of the immunopathogenesis of DM and PM.[35,97-99] Innate immune responses are characterised by plasmacytoid dendritic cell infiltration and IFN alpha/beta expression, and both features are associated with DM.[35,100] Many IFN inducible genes are overexpressed in juvenile DM patients,[101] and IFN-alpha expression correlates inversely with the duration of untreated disease.[99]

Chemokines

Chemotactic cytokines termed chemokines regulate selective leucocyte activation and migration. The IFN-gamma inducible alpha-chemokines CXCL9, CXCL10 and CXCL11 are elevated in IIM patients.[93,94,102] These chemokines have angiostatic properties and their expression correlates with the degree of capillary loss and inflammation in juvenile DM.[103] CXCL9 positive fibres are found in areas with severe inflammation in PM, but are very rare in DM.[94] Juvenile DM muscle contains significantly upregulated levels of CXCL13, a chemokine implicated in B cell organisation.[92] Upregulation of the beta-chemokines CCL2, CCL3 and CCL4 has been described in IIM patients,[93,94,104,105] and CCL2 in particular is viewed as one of the key disease regulators.[96,106-108] Strong CCL2 expression localises to CD8+ T cells actively invading non-necrotic muscle fibres of PM, and to blood vessels. On the one hand, CCL2 is upregulated locally on the blood vessel endothelium near inflammatory foci of PM, which may direct specific receptive leucocytes to the endomysial target sites and regulate the build-up of focal infiltrates. On the other hand, CCL2 is generally increased in blood vessels in DM tissues, also at sites remote from inflammatory cell collections. Its distribution mirrors other endotheliopathic changes that can be observed in DM blood vessels, which includes staining for TNF, ICAM-1 and membrane attack complex. CCL19 and CCL21, beta-chemokines involved in dendritic cell migration, are expressed by muscle fibres in PM tissues. The corresponding receptor CCR7 is present on inflammatory cells surrounding and invading non-necrotic muscle fibres and frequently these cells aggregate into nodules.[109]

CURRENT TREATMENT

Although there are data indicating that DM and PM can resolve spontaneously,[110,111] the general opinion is that patients with muscle weakness need treatment. Some data indicate that a longer disease duration before the start of immunosuppressive treatment is prognostically unfavourable.[112-115] However, sIBM was probably not well-identified and not excluded in these studies. Furthermore, there are also data showing no relationship between duration of illness until start of treatment and the occurrence or frequency of relapse.[116] The goals of therapy are to improve the ability to carry out activities of daily living by increasing muscle strength and to ameliorate extramuscular manifestations (rash, dyspnoea, arthralgia, and fever).

Corticosteroids

Initial high-dose corticosteroids (1 to 1.5 mg/kg prednisolone per day for at least four weeks) followed by slow tapering to prevent relapses are the treatment of choice on an empirical basis; its effect has not been investigated in an RCT.[1,117] In general, lack of high-quality RCTs assessing efficacy and toxicity of immunosuppressants characterises the field of IIM. A recent RCT compared oral dexamethasone pulse therapy (six cycles of 40 mg/day for four consecutive days at 28-day intervals) versus daily prednisolone (70 to 90 mg/day depending on the body weight) for 28 days, followed by a slow tapering regimen for 44 or 52 weeks (depending on the initial dose) in IIM. It was concluded that although pulsed high-dose oral dexamethasone is not superior to daily prednisolone as first-line treatment in IIM, it may be a good alternative by causing substantially fewer side effects in a broad range.[118]

Second-line treatment

If treatment with corticosteroids fails (because of too small an effect, repeated relapses, or unacceptable side effects), various second-line treatments are in use.[1,117] The small number of RCTs makes it difficult to decide which immunosuppressive agents are beneficial in PM and DM. Three studies compared immunosuppressants with placebo.[119-121] A non-statistically significant effect on muscle strength was found for azathioprine compared with placebo in patients treated with prednisone.[119] After three years of follow-up, those treated with the combination of prednisone plus azathioprine had improved more with respect to functional disability and required less

prednisone for disease control, but differences were small and not ascertained blindly.[122] A beneficial effect of intravenous immunoglobulins compared with placebo was found in patients with DM,[120] although muscle weakness reoccurred directly after stopping the infusion. These data were confirmed in a cross-over study among patients with DM.[123] In PM, no controlled studies on intravenous immunoglobulins have been completed. No benefit was shown of plasma exchange and leucapheresis.[121] One trial compared methotrexate with azathioprine in IIM,[124] and found equivalent efficacy but better tolerance of methotrexate. Another trial compared cyclosporine with methotrexate in PM and DM,[125] and found no statistically significant difference between the two groups. Intravenous methotrexate was compared with oral methotrexate plus azathioprine in a trial of refractory myositis,[126] and although no statistically significant difference between the two treatments was found, a trend favouring combination therapy was detected. In a study with historical controls among children with DM, use of methotrexate in conjunction with an aggressively tapered course of prednisone was as effective as traditional long-term corticosteroid therapy, while decreasing the cumulative dose of corticosteroids.[127]

In practice, most experience has been gathered with methotrexate (up to 25 mg/week) and azathioprine (up to 3 mg/kg/day). Intravenous immunoglobulins can have a short favourable effect in patients with DM. Other immunosuppressive drugs used in the treatment of PM and DM are cyclosporine (orally, 100 to 150 mg twice daily),[128] which may also benefit childhood DM.[129] Mycophenelate mofetil (2 gram per day) is emerging as a promising and well-tolerated drug.[130] Cyclophosphamide (0.5 to 1.0 g/m^2) intravenously has shown mixed results;[131,132] it may be useful in case of ILD, but the evidence remains circumstantial.[133]

ILD can occur with DM and PM.[134,135] There are no controlled studies on the best treatment for DM or PM complicated by ILD. In several case series favourable results are mentioned for treatment with corticosteroids with or without other immunosuppressants such as azathioprine, cyclophosphamide, cyclosporine and tacrolimus.[133,136-144]

FUTURE THERAPEUTIC PROSPECTS

Given the fact that use of chronic immunosuppressive therapy is associated with significant side effects, and many patients remain partially refractory to treatment, the discovery of novel therapeutic agents that are safe and effective for DM and PM is highly desirable. Improvements in treatment for IIM are hampered, however, by difficulties in the design of trials and the low incidence and prevalence of the disease.[13] Furthermore, the disease-specific outcome measures used differ between studies, which impedes comparison of results.

Anti-TNF therapy

Preliminary case reports show in general successful treatment of refractory DM and PM with anti-TNF treatment.[145-153] In five juvenile refractory dermatomyositis patients, major clinical benefit was demonstrated after the initiation of anti-TNF therapy.[154] However, an open-label study of TNF blockade combined with weekly methotrexate in six drug-naive patients with DM and PM was terminated prematurely because of the low inclusion rate and high dropout rate due to disease progression and the occurrence of an infusion reaction. The two patients who did reach the primary endpoint showed improvement in all aspects studied.[60] Furthermore, in an open pilot study, treatment with an TNF inhibitor was not effective in 13 patients with refractory IIM.[155] In addition, onset of myositis has been reported in patients with arthritis during treatment with anti-TNF therapy.[156,157] Lymphotoxins (LTs), cytokines related to TNF, represent other amenable targets for treating IIM. In this respect, soluble LT-betaR-Ig fusion protein, a potent blocker of the LT signalling pathway,[158] might be worth exploring in the future.

Anti-B-cell therapy

B-cells may play a pivotal role in the pathophysiology of IIM. As recently reviewed, early uncontrolled clinical experience indicates that B-cell depletion with rituximab (a monoclonal antibody targeting CD20 antigen on B lymphocytes) may be a valuable therapeutic approach for treatment of refractory IIM.[159,160] A few case reports indicate beneficial effects of rituximab in patients with the anti-synthetase syndrome.[161,162] Further investigation regarding the optimal dosing regimen, treatment length, and long-term safety profile of rituximab therapy for IIM is, however, warranted. In addition to rituximab, second- and third-generation anti-CD 20 monoclonal antibodies[163] and agents that target B-cell growth factors, such as B cell activating factor belonging to the TNF family (BAFF) and a proliferation-inducing ligand (APRIL), could have promise for the treatment of myositis, and might be explored in this setting.[164]

Anti-IFN-alpha treatment

Another approach to new treatments for DM and PM would be the development of monoclonal antibodies that neutralise human IFN-alpha. Preliminary results using sifalimumab (an anti-IFN-alpha monoclonal antibody) in a single-dose phase-I trial among subjects with systemic lupus erythematosus showed sifalimumab-specific and dose-dependent inhibition of the overexpression of type I IFN-inducible mRNAs in the blood of treated subjects.[165]

Other anti-cytokine therapies and anti-chemokine therapy

The prominent role played by other cytokines and chemokines, as mentioned before, makes them attractive targets for selective anti-inflammatory therapy. Chemokines with key roles in the immunopathogenesis could be neutralised by administering antibodies that abrogate chemokine-chemokine receptor interactions, inactivating chemokine analogues, or small molecule pharmaceuticals that antagonise receptor function.[166] No chemokine-based strategies have been tested in IIM as yet.

OUTCOME MEASUREMENT

An international, interdisciplinary network, the International Myositis Assessment Clinical Study Group (IMACS), has proposed a core set of outcome measures to be used in clinical trials to assess three dimensions of myositis disease: disease activity (MYOACT), disease damage (MYODAM) and health-related quality of life (SF-36).[167] Use of these outcome measures will help in validly comparing results of clinical trials among patients with IIM.

CONCLUSION

IIM have a presumed autoimmune pathogenesis. PM and DM may occur in isolation or in connection with a CTD or cancer. The current treatment of IIM consists of first-line high-dose steroids and various conventional second-line treatments. Improvements in treatment for IIM are hampered by difficulty in the design of trials and the low incidence and prevalence of the disease. Cytokines and chemokines are factors involved in the inflammatory process in IIM and are candidates for future therapeutic targets, as is anti B-cell therapy. Outcome measures to be used in clinical trials in IIM include at present the core sets of outcome proposed by the IMACS.

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