CURRENT PHARMACOLOGICAL TREATMENT OF IDIOPATHIC INFLAMMATORY MYOPATHIES

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Abstract

The idiopathic inflammatory myopathies are uncommon and heterogeneous disorders. Their classification is based on distinct clinicopathologic features. Although idiopathic inflammatory myopathies share some similarities, different subtypes may have variable responses to therapy, so it is very important to distinguish the correct subtype.

There are few randomised, double blind placebo controlled studies to support the current treatment. High dose corticosteroids continue to be the first line therapy and other immunosupressive drugs are used in refractory cases, as well as steroid-sparing agents.

Some novel therapeutic approaches have emerged as potential treatment including tacrolimus, intravenous immunoglobulin and rituximab, following good outcomes reported in case studies. However, more randomised controlled trials are needed.

This review considers the current and the potential future therapies for inflammatory myopathies.

Keywords:

Idiopathic inflammatory myopathy, treatment, dermatomyositis, polymyositis, inclusion body myositis

Introduction

The idiopathic inflammatory myopathies (IIM), including dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (NM) [1-13] are heterogeneous conditions [1,3-6,13-17]. Their precise aetiology is unknown and they are characterized by muscle weakness and inflammation, combined with elevated muscle enzymes and characteristic changes on electromyography and muscle biopsy [1,5,17-19].

Some patients with inflammatory muscle disease may have a range of other autoimmune rheumatic conditions, including Systemic Lupus Erythematosus (SLE), Rheumatoid arthritis (RA), scleroderma. These patients are often referred to as overlap myositis and should be distinguished in context, for example, when selecting patients for clinical trials.

These conditions are potentially treatable, but an early and correct diagnosis and institution of treatment are needed [10, 20, 21].

There are few randomized studies to support the current treatment paradigm [2-4, 19, 20, 22, 23] which is still based primarily on clinical experience [2-4, 11, 16]. First-line therapy is invariably corticosteroids, [1, 3-7, 16, 17, 19-22, 24, 25] although there are no adequate randomized controlled trials to support this [3, 6, 9, 13, 17]. Other immunosupressives, notably azathioprine and methotrexate, are widely used as second-line agents in refractory cases or as steroid-sparing agents [1,3, 4, 6, 7, 9, 15, 16, 18-21, 25,26].

DM, PM and NM usually have a good response to treatment with immunosuppressives [2, 10, 19, 20], but IBM is frequently resistant to these drugs, remaining a treatment challenge [2, 9, 10, 19, 27].

The first key to successful treatment is a correct diagnosis [18]. When a patient with DM or PM is not responding to immunosuppressive treatment, physicians must not be afraid to ask themselves if the diagnosis is wrong [3, 6, 15, 16], before considering other therapeutic options [6, 15, 16].

A critical part of the evaluation of a patient with myositis is to distinguish between ‘disease activity’ which is a reversible process due to inflammatory changes that might respond to immunosuppressive treatment and ‘disease damage’ which is a persistent/permanent change in physiology, pathology or function, that will not respond to this treatment. Common diagnostic approaches include directed

physical examination, laboratory testing, MRI, repeated muscle biopsies and the use of IMACS tools [14].

Other approaches such as intravenous immunoglobulin and rituximab have emerged as potential treatments for patients with myositis [9], but more randomized controlled trials are needed.

CORTICOSTEROIDS

High dose corticosteroids remain widely used [1, 3-7, 15, 16, 19-22, 24, 25]. Although widely prescribed as initial therapy of 1 mg/kg per day for a month, this dosage of prednisolone is probably unnecessary; our group, for example, uses 0.5mg/Kg/day. The dose is then gradually tapered within several weeks to the minimum maintenance dose to keep the disease controlled [6, 17-21]. The rate of taper is dependent on the patient's clinical response [2,6].

In severe cases, at the onset, methylprednisolone is used intravenously up to 1g per day, for 3-5 days [6,17, 18, 20].

Response to corticosteroids should be evaluated by monitoring strength, serum muscle enzyme levels and repeat imaging [6, 18, 19]. It should be stressed that a simple reduction in muscle enzyme levels may be an insufficient guide to therapeutic response.

Most patients with PM or DM have a (partial) response to corticosteroids [19]. However, in IBM prednisone is usually not effective, although some patients may improve temporarily [2 ,6, 11, 13, 19].

The great concern about the use of high doses steroids is its major side effects. These include osteoporosis, increased risk of infections, diabetes and hypertension. There is an increased risk of a fracture in patients on more than 5mg/day [2]. Steroids should be accompanied by 1000 mg calcium carbonate and 400-500 IU vitamin D per day [2, 17]. Pneumococcal and flu vaccine should be recommended [17, 28], ideally before starting therapy or during stable disease [28].

Another important side effect of glucocorticosteroids is the steroid-induced myopathy that can mimic a relapse [2,19].

A recent randomized controlled study compared oral dexamethasone pulse therapy (six monthly cycles of 40mg/day for four consecutive days) with oral daily prednisolone (70-90mg per day for one

month with slow taper for 44-52 weeks) and found no difference in efficacy. However, high dose dexamethasone causes substantially fewer side effects [17, 19, 21, 25], but has a shorter median time to relapse [25,29].

Immunosuppressive therapy

Second-line immunosupressive agents should be added to corticosteroids in refractory cases or as steroid-sparing agents [1-4, 6, 7, 9, 15, 16, 18-22, 25, 26] or commenced at the same time in severe disease [2, 18]. There is no established time to begin steroids sparing agents, it is dependent on the response, side effects and inability to taper the steroid dose and the activity of the disease, especially if there is pulmonary/ pharyngeal involvement [19].

There are limited data about which agent should be used [18, 21, 25], but the choice includes azathioprine, methotrexate, intravenous immunoglobulin, mycophenolate mofetil and cyclophosphamide [18].

The commonly used immunosuppresive drugs may exert both a "steroid-sparing" effect (non evidence based) [10, 11, 13, 22], and provide a modest benefit themselves [10, 11, 13]. Monitoring of these potential powerful drugs is essential and includes regular (often every 4-8 weeks) blood tests, checking the full blood count, urea, electrolytes and liver function tests and, where available, serum drug levels (e.g. MMF) should also be undertaken [22].

Immunosuppressant drugs are generally ineffective in IBM [6].

In DM patients the use of topical agents such as tacrolimus, hydroxychloroquine and corticosteroids is recommended, as well as sunlight avoidance [6,19].

<u>METHOTREXATE (MTX)</u>

MTX is given as a weekly maintenance dose of 7.5–25 mg [2, 17, 18, 20]. It can be administered orally or subcutaneously [18].

Common side effects include increase of the liver enzymes [2, 17, 18, 20] and myelosupression [17, 18, 20], which should be monitored with laboratory tests. Therapy with MTX should be avoided in

patients with pulmonary involvement (interstitial lung disease) as MTX may on occasions cause pulmonary infiltrates [20].

MTX interferes in the folate metabolism, so folic acid supplement should be given to avoid toxicity [2, 17].

Response to methotrexate is likely to occur up to 3 months after starting therapy [17, 18].

Retrospective studies have shown MTX efficacy in DM and PM.[20]One randomized study comparing MTX versus placebo in IBM showed a significant decrease of the CK, but no change in disease progression [2,19].

A trial comparing MTX with azathioprine in idiopathic inflammatory myopathy found equivalent efficacy, but MTX was better tolerated. Another trial compared cyclosporine with MTX in PM and DM and showed no statistically significant difference between the two [21].

Studies comparing methotrexate versus azathioprine, methotrexate versus cyclosporine and intramuscular methotrexate versus oral methotrexate plus azathioprine, showed no statistically difference in efficacy between the regimes [25].

AZATHIOPRINE (AZA)

This drug is usually started at 50 mg/day for a week, and then increased weekly to 2-3 mg/kg/day [2, 17, 18].

Bone marrow suppression is the major potential (although very uncommon) side effect of AZA [2, 18], especially in patients with thiopurine-methyl-transferase deficiency. This enzyme activity should be measured, before starting the treatment [2, 17]. Increased liver enzymes may also occur [2,18]. During treatment with AZA, it is essential to check the blood count and liver enzymes, approximately every 6 weeks [2, 17, 18, 20]. If liver enzymes are markedly increased (2x above the normal range), AZA should be stopped until the enzymes normalize. If the leucocytes are below 250/μl or the absolute neutrophil count is below 1,000, it should be stopped [17].

Gastrointestinal toxicity (nausea, abdominal pain, vomiting and anorexia) may occur, but pulmonary toxicity is rare making AZA an appropriate choice for patients with pulmonary involvement [18].

Angiotensin converting enzyme inhibitors should be avoided because of the risk of severe leucopoenia, and concomitant allopurinol requires a dose reduction of 25-33% [17].

And open-label follow-up of a prospective double-blind study and some retrospective studies have shown that AZA is effective in DM and PM [20].

Response to AZA often takes some months to occur. The peak is at 1-2 years [17]. This delay may explain why in a small controlled study comparing AZA (2mg/Kg/day) plus oral corticosteroids versus steroid alone, there was no improvement in CK levels or weakness with AZA at 3 months [17, 19, 21]. However, after three years of "unblinded" follow-up, the AZA group had improved functional outcomes and lower doses of maintenance prednisolone [19, 21].

In fact, combination therapy (AZA + prednisolone) seems to reduce the risk of relapse as well as improve long-term outcome. DM and PM patients who have pulmonary involvement (ILD), alone or as part of as anti-synthetase syndrome, may benefit from an initial combination therapy (with AZA and prednisolone) [20].

In a randomised double blind controlled trial comparing the use of methotrexate and steroids versus azathioprine and steroids, in the treatment of IIM, there was no difference between the two groups [17,30].

MYCOPHENOLATE MOFETIL (MMF)

MMF is an anti-metabolite that blocks "de novo" purine synthesis and targets the production of activated B and T lymphocytes and fibroblasts [31].

MMF is administered orally, with a starting dosage of 500mg twice daily, which can be increased to 2-3g/day [2, 18]. Side effects include kidney and liver toxicity, but these occur less frequently than with compared to MTX or AZT [2]. Gastrointestinal intolerance (diarrhoea) and leucopoenia are also important [2, 18].

A response to MMF should be seen within 2-3 months [18].

MMF is emerging as a promising drug [19, 21], especially when used in refractory IIM [3,4,19,32] (including refractory rash [3,4]) and in patients with ILD refractory to steroids [4,17, 31].

Small case series have shown objective muscle strength improvement in IBM treated with MMF [19].

The use of MMF in severe cases of adult or juvenile myositis has been supported by uncontrolled trials [5].

CYCLOSPORIN A (CSA)

This drug is usually administered in divided doses, orally, from 3 to 5 mg/Kg/day [18,21].

Its major side effects are liver [2,18] and kidney toxicity [2, 17, 18], as well as, bone marrow suppression [18] and hypertension [17,18].

A response should be seen within a few months [18].

CSA may be used to treat patients with PM or DM who have failed to respond adequately to corticosteroids [26]. It may also be useful in childhood DM [21].

In patients with pulmonary involvement refractory to steroids and with anti-Jo1 anti-synthetase syndrome, combination therapy with CSA has been shown to be safe, invariably, and as effective as second line agent [17].

CYCLOPHOSPHAMIDE (CyC)

CyC is a third line drug [17] which is administered as monthly infusions pulses ($1g/m^2$) [18, 19] or as daily therapy orally (1-2mg/kg/day) [33] and may be used in combination with corticosteroids [31].

CyC is less used due in part to its side effects [2,33], notably alopecia, haemorrhagic cystitis, sterility, teratogenicity, increased risk of infection and malignancy [18]. However, monthly intravenous CyC is associated with fewer adverse effects than daily oral administration [31].

It is reserved for IMM patients refractory to most other therapies [2, 20], especially in those with associated ILD [17, 19, 34, 35] and severe or refractory juvenile dermatomyositis [5].

Several case studies demonstrate the efficacy of treatment with CyC in PM/DM patients [31]. The combination therapy of CyC and corticosteroids was effective on pulmonary function in IIM patients with severe pulmonary involvement [33].

A study of 9 patients with PM and DM treated with intravenous pulse of CyC reported improvement and sustained response of the majority of the patients [36].

Tacrolimus (TAC)

Tacrolimus, a third line drug, [17] is administered orally, up to 2-3mg twice daily. Common side effects are increased susceptibility to infection, alopecia, skin erythema, pruritus, gastrointestinal symptoms (constipation, diarrhoea and nausea), hypertension, renal and hematologic toxicity [18].

TAC acts as calcineurin inhibitor and suppresses T lymphocytes secreting cytokines, such as interleukin-2 [37].

Several case series and retrospective studies demonstrated TAC efficacy and tolerability in anti-synthetase/ SRP antibody-positive patients [3,5 19] and also in others refractory patients,[17,19] including patients with ILD [4,17,31,34].

One prospective, open, non-randomized study of 9 patients with PM/DM has shown benefit in the majority of patients refractory to previous therapy [38].

In a retrospective study of 15 patients with PM/DM who had received oral TAC in addition to corticosteroids an improvement of muscle strength and CK levels was shown and also an accelerated tapering of corticosteroids [37].

A Japanese retrospective study of 49 patients with IIM and ILD has shown significantly longer event-free and disease-free survival of the patients treated with TAC (25 patients) compared with those treated with other conventional agents. Outcome events were defined as severe adverse event, death or relapse of respiratory cause. Although this study has some limitations, it provides an incentive to the use of TAC in moderate/ severe IIM with pulmonary involvement [39,40, 41].

Intravenous Immunoglobulin (IVIG)

IVIG has been used and reported to be effective in refractory/ severe disease.[1,2,6, 16, 19, 20, 26, 34, 42] It is often “turned to” when side effects from immunosuppressives outweigh their clinical benefit [1, 15, 16]. It seems to have good outcome in associated ILD [1,20,34] and oesophageal involvement [1, 15, 16, 43].

Its use remains expensive, controversial [19] and needs to be individualized [20].

The initial dosage is 2-3g/Kg, as divided doses, often spread over 3 days and repeated every 4-8 weeks [2,18].

There are some important side effects such as increased risk of thrombosis [2, 17, 44] allergic reactions/anaphylaxis and fever [2, 17]. An immunoglobulin A deficiency should be excluded before starting the treatment, because these patients have an increased risk for allergic reactions [2, 17].

IVIG appears to be safe during pregnancy [1,2].

In controlled prospective studies, IVIG had improved dysphagia [45,46,47] , but had no impact in increasing of the limb strength [47-50].

In a case study, an IBM patient was reported to have had beneficial effects from low dose IVIG [1, 27].

A retrospective study reported 8 patients with juvenile dermatomyositis, who were able to avoid steroids with combined therapy with IVIG and immunosuppressives including methotrexate. This is important to avoid prolonged exposure to steroids, especially in paediatric population [1, 51].

A study of 7 patients with refractory PM or DM used subcutaneous immunoglobulin, at home by programmable pump, reported good response to treatment. The 2g/kg/month dose of IVIG was equally fractioned in weekly subcutaneous doses. This method could be a safe, practical and also cheaper alternative, but more studies are needed [1, 17,52].

If the patient is not responding to corticosteroids and IVIG, the diagnosis should be questioned and another muscle biopsy and an extended panel of myositis autoantibodies should be tested [6].

A hereditary myopathy must be excluded. If the diagnosis of IIM is confirmed, experimental treatment such as biologic agents should be considered [6].

Biologic therapy

Advances in our understanding of the inflammatory pathways involved have suggested alternative therapies for patients with myositis inadequately responding to prednisone and other conventional immunosuppressive drugs. New biological agents in the form of monoclonal antibodies or fusion proteins selectively targeting B cells or T cells, cytokines and co-stimulatory or transduction molecules, are emerging as a promising option for refractory cases and may change the current outcome of myositis.

B-cell blockade

RITUXIMAB (RTX)

The chimeric monoclonal antibody RTX selectively depletes B-cells. It targets the CD20 antigen, present on the surface of immature memory B cells and B cells in the germinal centre, but not on pro-B cells, early pre-B cells and plasma cells. It is approved for treating non-Hodgkin's lymphoma, rheumatoid arthritis (RA), granulomatosis with polyangiitis and microscopic polyangiitis. It has also shown efficacy in treating other autoimmune diseases. Currently, RTX is the most promising biological therapy for refractory myositis. Several case series reported that RTX at 2 g (two infusions at a dose of 1000 mg, given two weeks apart) or 375 mg/m2 weekly for 4 consecutive weeks, can be of benefit in some disease subsets.

In 2005, Levine *et al* [53] first described the use of RTX in six patients with DM resistant to conventional treatment. Improvement in muscle disease and skin lesions was observed in each patient, although four of them had disease relapse, coinciding with the return of B cells. Since then, there have been several other reports of beneficial effects of RTX in patients with myositis. In terms of PM, B-cell depleting therapy has shown efficacy, even in refractory subsets such as those patients with anti-signal recognition particle (SRP) antibody positive NM [54, 55]. RTX has also demonstrated efficacy in patients with DM with improvement of both muscle and skin disease [56, 57], although other studies reported limited response in patients with refractory skin involvement [58, 59]. Beneficial effects of RTX have been described in patients with juvenile DM [60, 61] and with anti-synthetase syndrome (ASS) [62, 63].

Based on these promising results, the efficacy of RTX was tested in a randomized, double-blind, placebo-phase trial in adult and paediatric myositis. The 'Rituximab In Myositis' (RIM) trial [64] was conducted in 200 patients with refractory myositis treated for 44 weeks with different regimen of RTX (96 patients received 2 infusions at baseline whereas 104 patients received RTX 8 weeks later). Refractory disease was defined as failure to respond to steroids and at least one immunosuppressive agent. Although there was no significant difference in response time between the two treatment arms (primary endpoint), at week 44 an 83% success rate and a significant steroid-sparing effect were achieved in both groups.

Possible reasons for the failure of the RIM trial include the study design (notably the choice of a too short 'placebo phase' duration based on ethical considerations and the power calculation based on the premise that RTX had an early onset of action by 8 weeks), the use of a only partially validated core set of measures and the heterogeneity of myositis [65]. A post-hoc analysis of the subgroups in the RIM study showed that patients with the positivity of myositis-specific autoantibodies (mainly anti–Jo-1 and anti–Mi-2 antibodies) seem more likely to have a clinical response to RTX [66]. Thus, there remains a belief that B cell depletion may be effective in autoantibody producing subjects, but there is little point in using RTX in the almost 20% of IIM patients with no definable myositis autoantibodies. The failure of RIM trial highlighted the need to develop new myositis response criteria which can predict outcomes more accurately and more careful planed studies are needed for further trials.

T-cell blockade

ABATACEPT

Abatacept is a fusion protein containing the cytotoxic T lymphocyte antigen 4 (CTLA-4), a physiological antagonist of the co-stimulatory protein CD 28 on T cells, fused to the Fc region of a human immunoglobulin G1 (IgG1). Histopathological studies suggested that T cells may play a role in the pathogenesis of myositis due to the demonstration of infiltrating T lymphocytes and the expression of CD28 and CTLA-4 ligands in biopsies of patients with PM [67].

There are three case reports showing beneficial effects of T cell blockade in myositis. Musuruana *et al.* [68] first introduced abatacept in a 51-year-old female patient with PM refractory to conventional treatment. At the last clinical evaluation, 3 years with abatacept, her myositis symptoms were attenuated (her muscle strength was normal in her neck extensors and upper limbs, although she required leg braces to walk); her CK serum levels were slightly altered and her aldolase was within the normal range.

Later, an improvement in muscle and skin disease was reported in a patient with juvenile DM complicated by ulceration and calcinosis [69]. Recently, Kerola *et al.* [70] reported a case of a 46-year-old female patient who developed a severe myositis overlap syndrome, including features of RA, peripheral vasculitis and ILD, refractory to different immunosuppressive and biologic drugs.

After a few infusions of abatacept, her serum CK was in the normal range. An improvement of her muscle strength was also observed, although her physical capacity was reduced due to disease damage. Based on these case reports, abatacept may be a potential option to be considered in refractory myositis. A phase II randomized clinical trial (ARTEMIS study) is underway to test this hypothesis. [71]

Tumor necrosis factor blockade

INFLIXIMAB

Infliximab is a chimeric monoclonal antibody against the tumor necrosis factor α (TNFα). The rationale for using TNFα blockade in myositis is the up-regulation of TNFα and its receptor in muscle tissue of these patients and also the expression of this cytokine in the endothelium of subjects with DM [72]. Preliminary reports [73, 74] have shown an improvement in myositis after anti-TNF-α treatment. However, the results are conflicting. A pilot study conducted in 13 patients with refractory IIMs treated with infliximab reported no benefit [75]. MMT (manual muscle testing) did not improve in any patient. The lack of improvement in muscle strength was associated with persistent signs of inflammation in muscle biopsies or on MRI of thigh muscles. Similar results were reported in an open-label trial of infliximab combined with weekly methotrexate in drug-naive patients [76], which was terminated prematurely because of a difficulty in recruiting cases, due to disease progression and the occurrence of adverse events. Thus, at present, the use of infliximab in patients with treatment-resistant myositis is not recommended.

ADALIMUMAB

Adalimumab is a fully human monoclonal antibody against TNF-α. In the available literature, we could only find one case report of the use of adalimumab in IIM patients. Da Silva et al [77] described a case of 49-year-old female patient with ASS which did not adequately respond to different immunosuppressive drugs. The authors reported that adalimumab was introduced to their patient because of a previous incorrect diagnosis of RA. Interestingly, adalimumab improved significantly her muscle strength and her arthritis, normalized her serum muscle enzymes completely and stopped

the progression of ASS-associated ILD. Further investigations are needed to confirm the efficacy of adalimumab in myositis.

ETANERCEPT

Etanercept is a fusion protein of TNF receptor bound to a constant portion of human IgG1.

Sprott *et al.* [78] first reported the use of etanercept in a 50-year-old female patient with PM refractory to steroids and to immunosuppressive drugs. The patient showed a rapid improvement in her muscle strength and serum CK levels, and her daily prednisolone dose was slowly reduced and stopped. In 2006, Efthimiou *et al.* [79] published the results of six patients treated with etanercept, one with infliximab and one received sequential therapy with these drugs. Improvement of muscle strength and a decrease in serum levels of muscle enzymes was observed in six of the 8 patients. The main concern with this report is the combination of therapies with corticosteroids, immunosuppressive drugs and IVIG, which complicates the interpretation of which was the most helpful. This positive result was not confirmed by a 52-week pilot trial of etanercept compared to placebo [80] conducted in 16 treatment-naïve patients with myositis. Although no statistically significant differences between treatment groups were found using the "International Myositis Assessment and Clinical Studies Group- definition of improvement" (IMACS - DOI) [81], etanercept demonstrated a significant steroid-sparing effect. In addition, at the end of the study etanercept-treated patients showed improvement of many IMACS criteria including the manual muscle testing, physician global and Health Assessment Questionnaire. The reasons why the study failed to achieve its primary efficacy endpoint may be the low number of patients and the high drop-out rate, supporting the need for larger controlled trials to substantiate the efficacy of TNF inhibitors in the treatment of myositis.

Etanercept is not currently recommended for treatment of myositis.

Interleukin-6 blockade

TOCILIZUMAB

The rationale for using Interleukin-6 (IL-6) blockade in patients with myositis is the over-expression of IL-6 in muscle tissue and in the sera of patients with myositis [82, 83].

Our literature review identified only three case reports of the use of tocilizumab in myositis. In a first study, two patients with PM resistant to conventional treatment [84] have showed improvement in their clinical and laboratory findings after treatment with tocilizumab.

Later, Kondo *et al.* reported a case of a 32-year-old Japanese woman with refractory overlap syndrome, manifesting with DM, scleroderma and RA [85]. After treatment with tocilizumab, she was asymptomatic and her serum CK was normal. These preliminary data support the need for further investigations and a randomized clinical trial is underway to test this hypothesis [86].

Interleukin-1 blockade

ANAKINRA

The production of Interleukin-1 (IL-1) by activated macrophages, endothelial cells and muscle fibres is increased in IIM and can mediate the muscle damage [87].

A 12-month open-label study with anakinra, which inhibits activities of both IL-1α and IL-1β, reported an improvement in seven out of 15 patients with refractory myositis [88].

Interestingly, the inflammatory infiltrates were still present in repeat muscle biopsies and the IL-1 expression was not correlated to clinical response. However, in the sera of these patients a shift of differentiation of T cells from T helper 17 to T helper 1 was reported, suggesting a systemic effect of anakinra.

These preliminary results support the idea that the IL-1 blockade may have a role in subgroups of myositis, but more studies are needed. Gevokizumab, a potent monoclonal antibody binding strongly to IL-1 beta, is currently being studied in a global clinical trial [89].

Type 1 IFN blockade

SIFALIMUMAB

A rationale to use sifalimumab, an interferon (IFN) α-blocking agent, in myositis, is the frequent observation of the type I IFN inducible proteins and the IFN-regulated chemokines in muscle biopsies and sera of patients with DM and PM [90].

In a first phase 1b clinical trial [91], sifalimumab showed a moderate suppression of cluster of genes induced by type I IFN, highly over-expressed in IIM patients compared to controls. Positive correlation between gene neutralization and improvement of muscle strength by MMT8 was also recorded. A follow-up study [92] reported a suppressive effect on T cell-related proteins and a reduction of T cells infiltration in the muscle of these patients by blocking type I IFN.

Physiotherapy and Exercise

Exercise was initially seen as potentially deleterious, but recently was shown to be safe and in some cases efficacious [8, 19, 32, 93-95]. Rehabilitation is an essential part of the treatment of myositis [2, 8, 14, 94, 96]. Exercises should be prescribed individually and according to patients' characteristics, notably disease activity, range of motion, manual muscle test or dynamometer measurements and cardiorespiratory capacity [94]. It is important to be aware that in severe cases the main role of physiotherapy is to maintain the adequate range of joints movement with passive exercises. Later, when the patient is getting better, active exercises can be used.

Exercise with resistance and active exercise has demonstrated improvement in muscle endurance and strength as well as aerobic capacity and functional ability, in IIM including IBM patients [8, 94]. Controlled and randomized trials have indicated that increased aerobic capacity could mediate improvement in health and decrement in disease activity. Muscle atrophy caused by muscle inflammation and systemic corticosteroids treatment can also be prevented by exercise [8].

Expert commentary:

Due to the lack of controlled trials to guide therapeutic decisions, the management of patients with myositis remains challenging. Unfortunately, progress has been slower than in other autoimmune diseases, because of the difficulty in conducting high quality trials, due to the rarity and heterogeneity of the disease. For these reasons, the choice of treatment in patients with IIM remains empirical. On the basis of clinical experience, most patients respond to an initial treatment with corticosteroids. In cases that fail to respond to treatment with steroids, immunosuppressive agents may provide a non evidence-based 'steroid-sparing' effect, but are often only partly effective.

In refractory cases, IVIG can be tried, based on a controlled study conducted in DM, followed by tacrolimus. RTX appears to be the most promising biologic agent. It showed beneficial effects in uncontrolled studies and in approximately 80% of patients in the RIM trial, although the primary and secondary endpoints were not met. IBM continues to be difficult to treat. Although a small number of patients with IBM may show an early partial response to steroids, they become resistant to most therapies and the disease slowly progresses.

In spite of two negative trials, there remains a belief that IVIG may offer a short-term clinical benefit in some patients with IBM which is difficult to capture with the measures used [47, 50, 97].

Further better-designed controlled trials, using validated response criteria, are needed to achieve the best treatment for patients with IIM, that can arrest the disease progression.

Five- year view:

The availability of new agents approved to treat other systemic diseases potentially promise that they will be investigated also for patients with refractory myositis. A wide spectrum of cytokines, chemokines and growth factors have been reported to be up-regulated in the peripheral blood and in muscle tissues of patients with myositis compared with controls [98]. These molecules are different among the disease subtypes, reflecting their distinct clinical phenotypes. Several agents could be of interest for future studies of myositis treatment, including: alemtuzumab, which is a monoclonal antibody targeting the glycoprotein CD52 and was reported effective in PM [99]; drugs that target B-cell growth factors, such as B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) [100]; anti-complement agents (eculizumab), for the treatment of DM which is caused by a complement mediated vasculopathy [101].

Moreover, the future in IIM therapy may also include regenerative therapies such as gene therapy or the use of stem cells [18,19], and bone marrow transplantation [18]. Despite some early successful haematopoietic stem cell transplantation (HSCT) studies in refractory IIM [102-105], in 2012 a case of a refractory juvenile DM woman with recurrent deterioration one year after HSCT was reported. Severe complications after HSCT are common and more studies are needed to identify eligibility

criteria, outcome predictors and the adequate regimen [106]. Plasma exchange and leucapheresis have shown no benefit [7, 21, 25] and there are significant side effects [25].

In conclusion, targeting the precise pathogenetic molecules might have a potential in the future therapeutic management of IIM. The identification of responsive patients and specific therapies targeting the correct myositis subset can potentially prevent incorrect use of biologics.

Key issues:

» High dose corticosteroids remain first line therapy.

» For severe cases, intravenous methylprednisolone (up to 1g/day) is used for 3-5 days.

» Long term therapy with corticosteroids should be minimized.

» Immunosupressive therapy should be considered if the disease is not controlled with minimal dose of corticosteroids alone or there is organ involvement.

» Second line agents (MTX, AZT, CsA) are used in refractory/ severe disease or as steroid-sparing agents.

» MMF and TAC are emerging as promising drugs. They are used especially in refractory IIM and in patients who experience side-effects from other treatments.

» Due to its side effects, CyC is reserved for IIM patients refractory to most other therapies. Some case studies have shown efficacy in patients with pulmonary involvement, when combined with corticosteroids.

» IVIG seems to have, apart from some partial improvement of muscle strength, good outcome in patients with pulmonary and oesophageal involvement.

» Biologic agents are emerging as new therapeutic approaches, however more randomised and controlled studies are needed

» Exercise is generally safe and efficacious.

References and recommended reading

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