

Established and new treatments of the idiopathic inflammatory myopathies: dermatomyositis and polymyositis

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Received on March 27, 2007; accepted in
revised form on October 2, 2007.

Clin Exp Rheumatol 2007; 25: 896-906.

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EXPERIMENTAL RHEUMATOLOGY 2007.

Key words: Myositis, glucocorticoids,
immunosuppressive agents, infliximab,
etanercept, adalimumab, rituximab.

Introduction

Dermatomyositis (DM) and polymyositis (PM) are chronic idiopathic inflammatory muscle diseases. The pathogenesis of these disorders is not yet fully elucidated, but humoral and cell-mediated immune responses are thought to play a central role in DM and PM, respectively. Clinically, they are characterized by symmetrical proximal muscle weakness and by variable extramuscular manifestations, while histology of the affected muscles usually shows various degrees of inflammation and damage. Raised serum levels of muscle enzymes and typical electromyography (EMG) findings (brief-duration, small-amplitude motor unit action potentials) are other features frequently found in the active stages of the diseases. Inclusion body myositis (IBM) is often classified among the inflammatory myopathies, but it differs from DM and PM for a number of important pathogenic and clinical features, including failure to respond to immunosuppressive medications.

The aim of this article was to critically review and summarize the evidence on established and novel treatments for adult-onset DM and PM derived from randomized controlled trials (RCT). In the absence of evidence from such trials, data from open studies and case reports have been reported. Abstract data 2002 through 2006, American College of Rheumatology and 2002 through 2007 European League against Rheumatism have been included if relevant, if sufficient information could be extracted with regard to diagnosis ascertainment, treatment modalities, and outcome measures, and if the reported data had not been published as a full paper.

Classification of DM and PM

DM and PM are still often classified, and sometimes diagnosed, using the 1975

Bohan and Peter criteria (Table I) (1). These criteria were originally developed for classification purposes, but their use as a diagnostic aid was also endorsed by the Authors. There is little doubt that these criteria have indeed proved useful both to define patient populations in clinical trials and as guidance in clinical practice. However, they do have some limitations that are important to appreciate in order to avoid diagnostic pitfalls. First, they have been validated against other connective tissue diseases, but not against other myopathies (2). Second, the items required for diagnosis are defined somehow loosely (3). Third, the definition of “probable” or “possible” myositis (which does not necessarily require histological confirmation) may easily result in disease misclassification, especially for PM (4). Fourth, and crucially, these criteria are conceptually misleading in considering DM a “PM

Table I. Bohan and Peter criteria for the classification of DM and PM (1).

1. Symmetrical weakness of the limb girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement.
2. Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemmal nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and inflammatory exudate, often perivascular.
3. Elevation in serum of skeletal muscle enzymes, particularly the CK and often aldolase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) and lactate dehydrogenase (LDH).
4. Electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre, high frequency repetitive discharges.
5. Any one of the characteristic dermatologic features of the rash of DM.

Competing interests: none declared.

without a rash" (5) and, conversely, in labeling as PM any inflammatory myopathy without a skin rash. In fact, DM is a separate disease with a pathogenesis different from that of PM, while conditions such as IBM and myositis associated with connective tissue diseases (CTD), which would all be classified as PM according to the Bohan and Peter criteria, are distinct from PM in terms of pathogenesis, histology, and clinical features (6). Therefore, to avoid patient misclassification and misdiagnosis, a thorough workup including evaluation of muscle histology is required. From a practical point of view, it is particularly important to discriminate between those conditions that respond to immunosuppressive therapy, such as DM and PM, from those that do not, such as IBM.

Treatment of the inflammatory myopathies

Glucocorticoids

Glucocorticoids (GC) remain the cornerstone in the treatment of myositis, although their use has never been formally evaluated in RCT versus placebo. Lower-dose (7.5 to 30 mg/day, equivalent to < 0.5 mg/kg/day) prednisolone therapy has been shown in a single study to be as effective as higher-dose (40-100 mg/day, equivalent to > 0.5 mg/kg/day) prednisolone in terms of functional outcome and of decrease in muscle enzyme levels with a lower incidence of adverse events, but the retrospective and uncontrolled nature of this small (25 patients) study precludes a confident generalization of its results (7). Conversely, high-

dose GC pulse therapy (*e.g.* 500 mg methylprednisolone iv daily for three days) has been proposed as initial treatment for severe cases (8, 9). Although its use is not supported by evidence derived from RCT (10), the low toxicity of GC pulse therapy justifies in our view the use of this regimen early on in the disease course or upon relapses in severe cases. Pulse GC therapy could, at least theoretically, suppress more effectively inflammation through non-genomic mechanisms (mediated by high-dose GC), which are thought to operate via the stabilization of cell membrane with ensuing reduced activation of immune cells. In addition, GC pulse therapy could also act by inhibiting the synthesis of pro-inflammatory mediators via genomic mechanisms, which are activated by lower-dose GC (11). As a rule, however, a starting dose of 0.75 mg/kg/day of prednisone (corresponding to circa 40 to 60 mg per day) is considered adequate in most cases to control disease activity (12) (10). After 4-12 weeks, GC dosage can be gradually tapered *e.g.* in 20% decrements of the daily dose per month (12) while keeping patients monitored.

Some patients may not respond adequately to GC treatment or have relapses upon GC tapering. In these patients, immunosuppressive agents are thus often used to control disease activity, usually in combination with the lowest possible dose of GC. Furthermore, in patients that are at risk for GC-related side effects such as those with established osteoporosis, the addition of an

immunosuppressive agent to GC at the onset of therapy may be considered.

Second line agents

A number of second line agents have been proposed to treat the inflammatory myopathies, and the list of drugs available has been steadily growing over the past decades (Table II).

Azathioprine has been studied in a small RCT of three months' duration in 16 patients with previously untreated myositis (13). All patients received prednisone 60 mg daily plus either azathioprine (2 mg/kg/day) or placebo. Disease activity was assessed by serial creatine kinase (CK) measurements as well as by manual muscle testing (MMT) and by evaluation of histological muscle changes at the beginning and at the end of the study. The results of this trial were disappointing at three months, but in the open-label extension there was a significant improvement in muscle strength at one and three years and a GC sparing effect at three years in the azathioprine treated arm (12).

Another study investigated the efficacy of azathioprine (50 mg/day in escalating doses up to 150 mg/day from the third month onwards) in combination with oral methotrexate (7.5 mg/weekly in escalating doses up to 25 mg/weekly from the third month onwards) versus intravenous methotrexate (500 mg/m² every 2 weeks for 12 doses) and leucovorin rescue. Thirty patients with refractory myositis were randomized to either oral methotrexate and azathioprine or intravenous methotrexate and followed up for six months; crossover to the alternate therapy was permitted if the current treatment was ineffective or poorly tolerated. Prednisone was maintained for one month at the same dosage that the patients were taking before study entry, and then gradually tapered to attempt to achieve a dosage of 0.25 mg/kg every other day over the following five months. Of the fifteen patients randomized to initial oral treatment, ten (67%) completed the full six months of therapy, of whom eight had improved, one patient was unchanged, and one worse, while in the nine (60%) completers of the fifteen patients initially randomized to receive

Table II. Second line agents for the treatment of adult myositis

Drug	Dose	Main indications
Glucocorticoids	variable	All main manifestations of myositis
Azathioprine	2 mg/kg/day	Muscle disease, maintenance therapy of ILD
Cyclosporine	3-5 mg/kg/day	Muscle disease, maintenance therapy of ILD
Cyclophosphamide	300-800 mg/m ² monthly	Induction therapy of ILD, sometimes used in DM
Hydroxychloroquine	200-400 mg/day	Skin rash of DM
Methotrexate	7.5-20 mg/week	Muscle disease
Mycophenolate mofetil	1 gram twice daily	Muscle disease, maintenance therapy of ILD, rash of DM
Tacrolimus	0.075 mg/kg/day	ILD

DM: dermatomyositis; ILD: interstitial lung disease.

intravenous methotrexate, improvement was observed in four patients, no change in four, and worsening in one patient. This study lacked the power to compare both treatments, but intention-to-treat analysis showed a trend for a better outcome in patients receiving combination therapy (14).

The response to methotrexate was retrospectively evaluated by Bohan *et al.* in a cohort of GC-resistant myositis patients (15). A significant disease improvement could be attained in 88% patients, while 43% were able to reduce their GC dose.

In a more recent RCT of six month's duration, Vencovsky *et al.* compared cyclosporine and methotrexate in the treatment of thirty-six myositis patients (20 with DM and 16 with PM) (16). Seventeen and nineteen patients were randomly allocated to treatment with methotrexate (7.5 to 15 mg/weekly followed 48 hours later by folic acid supplementation) or cyclosporine (3 to 3.5 mg/kg/day), respectively. Prednisone was co-administered at an initial dosage of 0.5-1 mg/kg/day to all patients and tapered after four weeks according to the patient's status. Response to therapy was evaluated after one, three and six months using separate criteria, including serum CK levels, muscle endurance and function testing, clinical assessment and magnetic resonance imaging (MRI) of muscles. An improvement in the above parameters was observed in both groups, with a trend for a better response to treatment in the methotrexate compared to the cyclosporine group. The average time to clinical response was one and three months, and the time to significant CK level decrease was one and six months for the methotrexate and the cyclosporine arm, respectively. One limitation of this study is that it did not include a placebo group; in addition, disease activity was not monitored by MMT, the most widely used assessment tool for myositis, which hampers comparison with other trials. Adverse events reported in the above studies during treatment with azathioprine and methotrexate were on the whole not serious and comprised liver enzyme elevation, cytopenia, and infections.

Cyclosporine has also been reported as being effective as first-line agent without GC in ten patients with definite DM (eight idiopathic, one juvenile, and one paraneoplastic) diagnosed according to the Dalakas criteria (17). The initial therapeutic scheme consisted of 10 mg/kg/day for one month followed by a gradual reduction to achieve plasma concentrations of 200-300 ng/ml, but after the first two patients were treated, the initial dose was reduced to 5 mg/kg/day, presumably in view of the development of renal failure in one patient that had been treated with 10 mg/kg/day. The control group was represented by a historical series of patients treated with steroids and "rescue" medications (mainly azathioprine) if needed. Cyclosporine was stopped in three patients after 12-18 months because of complete remission, while the remaining patients were left on maintenance doses. Compared with the patients treated with steroids, cyclosporine-treated patients showed a shorter time to achieve partial (7.6 ± 4.6 versus 3.8 ± 2.6 weeks) and complete (23 ± 24 versus 8.6 ± 2.2 weeks) remission. Mycophenolate mofetil (MMF) has been shown to be effective after an average of six to eight weeks in improving muscle disease in DM and PM as well as the rash of DM at a dosage of circa 30 mg/kg/day (0.5 g twice daily, increasing to 1 g twice daily over 2-3 weeks) in a number of small open studies and case reports. More specifically, to date five published studies (PubMed Search until December, 2006) have reported on the use of MMF in 18 DM, 8 PM and 1 systemic lupus erythematosus-associated myositis patients that were refractory or intolerant to standard therapy (18-22). A favorable clinical response was noted in 15 out of 18 (83%) DM patients and in all other patients. Another study showed MMF to be effective on the skin manifestations of four DM patients recalcitrant to various medications including GC, hydroxychloroquine, and methotrexate (23). MMF appeared to be well tolerated, although one patient developed a B cell lymphoma of the central nervous system, one abnormal levels of liver enzymes (19) and one cytopenia (on

combination therapy with azathioprine) (21). These adverse events, however, resolved upon drug withdrawal.

There is limited experience on the use of cyclophosphamide for the treatment of myositis. Short-term cyclophosphamide pulses have been reported as being able to induce disease remission in four out of five cases of myositis refractory to GC therapy (two cases were also resistant to other aggressive therapies) (24). In another study on eleven patients with recalcitrant myositis, cyclophosphamide pulse therapy led to a significant improvement in one patient and to a modest improvement in five other patients out of the six that completed the predefined course of seven monthly intravenous infusions (25). Major complications included serious infections in two patients and death in one patient, which were felt to be possibly related to the use of cyclophosphamide.

Other agents that have been used in myositis are chlorambucil (26) and leflunomide (27), but the data on these agents is too limited to allow definite conclusions.

In order to maximize efficacy while reducing the risk of developing complications, combination therapy with various agents has been advocated for the treatment of myositis, according to a paradigm well established for rheumatoid arthritis. The combinations proposed include methotrexate associated with azathioprine (14), methotrexate and cyclosporine (28), MMF with tacrolimus (29), and intravenous immunoglobulins with cyclosporine (30), while it is already common practice to treat patients with a combination of GC and immunosuppressive therapy. In pursuit of this line of research, King's College Hospital (London, UK) is currently co-coordinating a RCT known as SELAM (SEcond Line Agents in Myositis) assessing the value of adding to GC cyclosporine, methotrexate or a combination of both.

Plasmapheresis and intravenous immunoglobulins

Plasmapheresis has been used to treat DM and PM in a controlled trial in conjunction with GC, but proved no better than GC alone (31). By contrast,

high-dose (2 g/kg/month) intravenous immunoglobulins (IVIG) given in association with prednisone (mean dose 25 mg daily) have been demonstrated in a RCT to significantly ameliorate both muscle strength and skin rash in fifteen biopsy-proven DM patients recalcitrant to conventional treatments (32). Eight patients were randomly allocated to receive monthly IVIG infusions or placebo for three months, with the option of crossing over to the alternative therapy for further three months. All patients initially assigned to IVIG treatment showed a significant improvement in muscle strength compared to none in the placebo group and, similarly, all four patients that crossed over to IVIG therapy responded very

well to treatment. Maximal improvement occurred mostly between the second and the third infusion and was paralleled by a marked decrease or normalization of CK levels and (in eight patients) by a clearance of the cutaneous rash. No serious adverse events occurred requiring suspension of therapy. In PM, no controlled studies have been carried out, but uncontrolled observations suggest that IVIG may be effective in up to 70% of patients (33). Dysphagia seems to respond particularly well to IVIG, and is thus considered by some Authors a prime indication for this therapy (34).

Biological agents

Biological agents have been tried so

far in a limited, but growing number of myositis patients in open studies and case reports.

The rationale for using TNF- α inhibitors is based on the evidence of TNF- α messenger RNA expression in the inflammatory cells from muscle specimens of myositis patients (35) as well as in the endothelial cells from muscle specimens of DM patients (36). In addition, raised serum levels of soluble TNF-receptor 1 and 2 have been demonstrated in patients with active DM and PM (37). Theoretically, local TNF- α production could contribute to sustained inflammation both by activating inflammatory cells and by inducing the expression of adhesion molecules on endothelial cells, thus favoring inflam-

Table III. Published studies on TNF- α inhibitors in adult myositis.

Study	Drug	Concomitant drugs	DM	PM	Outcome
Anandacoomarasamy 2005	Infliximab 5 mg/kg	Prednisone 10 mg day Mycophenolate 2 g	-	1	Marked improvement after 2 nd infusion
Dold 2007	Infliximab 5 mg/kg (n = 1) and 3 mg/kg (n = 1)	Hydroxychloroquine 200 mg twice daily, prednisone 60 mg/day and methotrexate 15 mg/week (n = 1), prednisone 60 mg/day and methotrexate 15 mg/week (n = 1)	2	-	Sustained response to treatment in both patients with improvement of muscle strength and of skin rash (in one patient with baseline skin involvement), decrease in CK levels. However, one patient developed aspiration pneumonia and lethal bacteremia
Efthimiou 2006	Etanercept (n = 6) Infliximab 3 mg/kg (n = 1)	Oral GC (n = 7), pulse methyl- prednisolone (n = 6), azathioprine (n = 3), methotrexate (n = 2), IVIG (n = 8)	3	5	6 improved, 1 with PM and 1 with DM did not improve
Hengstman 2003	Infliximab 10 mg/kg	none	1	1	Improved
Iannone 2006	Etanercept	Second line agents washed out 1 week before study entry; oral prednisone at a dose of 10-30 mg daily (n = 5)	5	-	Worsening of muscle disease with elevation of muscle enzymes, unchanged rash of DM
Korkmaz 2004	Infliximab 8 mg/kg	Pulse methylprednisolone, methotrexate 15 mg intravenously weekly	1	-	Improvement of muscle, dysphagia and hypoventilation
Labioche 2004	Infliximab 10 mg/kg	Prednisone 20 mg day, azathioprine 150 mg daily, methotrexate 30 mg weekly	-	1	Marked improvement
Marie 2005	Infliximab 5 mg/kg	Prednisone 20 mg day	-	1	Fatal Mycobacterium peregrinum pneumonia
Roddy 2002	Infliximab 5 mg/kg	Methotrexate 7.5 mg weekly	1	-	Skin disease not improved, Non-Hodgkin lymphoma
Sprott 2004	Etanercept	Prednisone 30 mg day		1	Marked improvement
Selva-O'Callaghan 2004	Infliximab 5 mg/kg	Prednisone 15 mg day, cyclosporine 5 mg/kg/day, methotrexate 7.5 mg weekly	1		Marked improvement
Wendling 2007	Infliximab 5 mg/kg	Methotrexate 15 mg/week	-	1	Mild improvement

DM: dermatomyositis; GC: glucocorticoids; PM: polymyositis.

matory cell trafficking into the affected muscles. On the other hand, on a note of caution, TNF- α has also been shown to be expressed by regenerating muscle fibers, raising the question of whether it may contribute to muscle regeneration (38).

To date, the use of infliximab and etanercept has been reported in published papers in thirteen (five PM and eight DM) and thirteen (six PM and seven DM) myositis patients, respectively (Table III) (39-50). One patient with DM received treatment with both agents (40). All patients but two (41) had proved resistant to therapy with GC and a variety of immunosuppressive agents; in five patients, cytotoxic agents were washed out one week prior to study entry (42). The diagnosis of myositis was confirmed by a positive muscle biopsy in all patients except one patient with clinical DM and PM, respectively (40); in one DM patient, the skin biopsy was consistent with DM, whereas the muscle biopsy was negative (46). Of the eleven PM patients treated with TNF- α inhibitors, nine improved, one did not respond favorably, and one developed a serious adverse event, while of the fifteen DM patients seven improved, six did not (five from the same case series, see below), and one developed a serious adverse event. Of the thirteen patients treated with infliximab, ten had a favorable response, one failed to respond (40), and two patients developed serious adverse events that precluded a confident evaluation of therapy efficacy (45, 46). One of the patients that had responded well to infliximab subsequently developed aspiration pneumonia with ensuing multi-organism bacteremia and eventually died (49). Of the thirteen patients that received etanercept, seven improved and six failed to do so. Of note, five non responders (all with a diagnosis of DM) were all part of the same case series (42) in which immunosuppressive drugs were washed out one week prior to study entry, suggesting that immunosuppressive drug withdrawal might have contributed to the poor response observed in this particular group.

Significant adverse events occurred in six patients. Two patients on etanercept

developed candida esophagitis and a splenic tumor (40), respectively, while four infliximab-treated patients developed peptic ulcer (39), B cell Non-Hodgkin lymphoma (46), fatal *Mycobacterium peregrinum* infection (45), and aspiration pneumonia with ensuing lethal multi-organism bacteremia (49), respectively. However, since these patients were also receiving other treatments, and since myositis is associated *per se* with an increased risk of developing tumors, the exact role of TNF- α inhibitors in determining these side effects remains open to debate.

Additional data on the use of TNF- α inhibitors in myositis has been reported in abstract form. Constantine reported four myositis patients that responded favorably to etanercept (51), Dinser reported one patient with myositis associated with systemic lupus erythematosus that improved on infliximab (52), whereas in a case series that included 5 PM and 4 DM patients only 1 PM patient had a significant response to infliximab (53). Finally, a severe DM flare characterized by rising CK levels and worsening of muscle weakness following the first infliximab (3.64 mg/kg given in two infusions) infusion has been reported in a woman that had failed to respond to GC, intravenous immunoglobulins, and numerous immunosuppressive agents (54).

Overall, the impression is that TNF- α blockade may prove beneficial at least in some myositis patients, including those refractory to conventional treatments, although reports of new onset of PM in a patient with rheumatoid arthritis after initiation of infliximab therapy (55) and of a severe flare of DM after the first infusion of infliximab (54) have prompted some concerns. Adverse events, particularly infections, are also a cause of concern. Finally, there are now more than twenty published cases in the literature where treatment with a TNF- α blocking agent has led to the rapid evolution of interstitial lung disease (ILD), typically in cases with pre-existing mild or asymptomatic ILD [summarized in (56)]. Optimal dosing, timing of administration, and definition of the role of TNF- α blockade in remission induction versus maintenance

are all outstanding issues that should be addressed in controlled, prospective trials.

Overall encouraging results have been published on the use of rituximab (RTX) for the treatment of patients with the anti-synthetase syndrome (altogether four patients) (57-59), DM (fifteen patients, two of whom were also Jo-1 positive) (59-61) and PM (six patients, one of whom was Jo-1 positive) (60, 62) (Table IV). A further paper reported marked improvement of skin manifestations in three DM patients (two with juvenile DM), while the efficacy of RTX for muscle disease could not be assessed as the patients had no significant weakness at study entry (63) (Table IV). All but one patient had failed multiple medications. Most patients had a significant improvement in muscle strength and a decrease in, or normalization of CK levels, although in one study CK levels remained stable in three of the four patients with raised baseline CK and increased in another patient (61). ILD as assessed by high-resolution computerized tomography (HRCT) scan and pulmonary function tests improved or stabilized (57, 58). Some DM patients had also an amelioration of their skin rash (59), while in another study on eight patients skin disease remained basically unchanged (61). Response to treatment appeared to be paralleled by B cell depletion, however, relapses did not invariably correlate with the return of B cells (60). RTX therapy was overall well tolerated, although one patient developed cellulitis judged to be possibly related to therapy (59). An additional study on RTX in myositis (published only in abstract form) reported that RTX (1g x 2) led to a significant improvement in two out of seven DM patients (64). The mechanism of action of RTX in myositis is not entirely clear, albeit an interference with the humoral response could be postulated to explain its efficacy in DM. With regard to PM the data available is too limited to arrive at tenable conclusions, however, it may be surmised that RTX might act by suppressing the antigen-presenting or co-stimulatory function of the B cells with a downstream inhibitory effect on T cells.

Table IV. Published studies on rituximab in adult myositis.

Study	Regimen	Concomitant drugs	Disease (no. of patients)	Outcome
Brulhart 2006	1 g x 2	Prednisone 10 mg daily Methotrexate 15 mg/week	Anti-synthetase syndrome (n = 1)	Myositis improved, resolution of HRCT features of ILD
Chung 2007	1 g x 2	Prednisone 10-40 mg/day (n = 5), methylprednisolone 16 mg/day (n = 1), mycophenolate (n = 1), methotrexate (n = 3), hydroxychloroquine (n = 1), azathioprine (n = 2), none (n = 1)	DM (n = 8)	50% or more improvement in muscle strength (n = 3), minor improvement in muscle strength (n = 3); overall stable skin disease; CK levels stable in 3 of the 4 patients with raised baseline levels, increased in the other patient
Dinh 2007	375 g/m ² 4 weekly	Cyclosporine 100 mg twice daily (n = 1), prednisolone 5 mg daily (n = 2)	DM (= 1), juvenile-onset DM (n = 1), juvenile DM (n = 1)	No patient had significant active muscle disease at baseline. Skin involvement markedly improved in all patients
Lambotte 2005	375 g/m ² 4 weekly	Prednisone 25 mg daily	Anti-synthetase syndrome (n = 1)	Myositis improved, DLCO stabilized
Levine 2005	375 g/m ² 4 biweekly	IVIG (n = 2), GC (n = 3), cyclophosphamide (n = 1), azathioprine (n = 3)	DM (n = 6), of whom 2 Jo-1 positive	Muscle strength improved by 50-60% (by 3-6 months), CK decreased, relapse heralded in 4/6 patients by increased number of B cells
Mok 2007	375 g/m ² 4 weekly	prednisone 2.5-20 mg/day (n = 4), mycophenolate (n = 3), tacrolimus (n = 1)	PM (n = 4), one of whom Jo-1 positive	Mild muscle strength improvement in two patients and normalization in two patients, CK drop in three patients and normalization in one patient
Noss 2005	1 g x 2	GC with methotrexate 40 mg/week (n = 1), GC and azathioprine (n = 1), prednisone up to 55 mg daily	PM (n = 2), DM (n = 1)	CK normalized after an average of 4.6 months, muscle strength improved in all and normalized in 2 patients

CK: creatine kinase; DLCO: diffusion capacity for carbon monoxide; HRCT: high-resolution computerized tomography scan; ILD: interstitial lung disease; IVIG: intravenous immunoglobulins; no.: number.

Adjunct therapies for myositis

Muscle damage is undoubtedly a major cause of muscle weakness, but the degree of weakness appears sometimes to be out of proportion to muscle damage particularly in early disease. One hypothesis is that muscle weakness and fatigue may be related, at least partially, to disturbances of the energetic muscle metabolism. This hypothesis is borne out by the demonstration of reduced levels of the muscle metabolites phosphocreatine and adenosine triphosphate in active myositis (65) (66). On a similar line, high levels of urinary creatine, most likely reflecting dysfunctional muscle metabolism, have been demonstrated in myositis patients (67). Conversely, creatine supplementation is generally considered to improve athletic and sporting performance. Based on this evidence, a recent RCT has aimed to investigate the efficacy of muscle exercise with and without creatine supplementation in 37 patients with DM and PM (68). The results of the trial showed

that both groups improved, with the magnitude of the benefit being significantly better in the creatine group. No flare of myositis occurred, in line with other observations that physical exercise is safe and effective in myositis patients (69, 70). Various studies indeed support the notion that exercise adapted to disease activity and disability improves function (70) and should be thus included in the rehabilitation of patients in all stages of myositis (71, 72). In particular, both resistive mild-moderate to intensive muscular training and aerobic endurance training (71, 72) have been shown to be of benefit to myositis patients without inducing disease flares.

Treatment of myositis subsets and of myositis associated with other conditions

Treatment of amyopathic dermatomyositis

There is limited data regarding how to treat patients with amyopathic DM (*i.e.*, patients with the typical skin manifes-

tation of DM but no evidence of muscle involvement). Most cases reported in the literature have been managed with low-dose GC, although the use of antimalarials such as hydroxychloroquine has also been advocated (73). It is currently unknown whether aggressive treatment of amyopathic DM patients may prevent transition to overt DM, but in view of the low prevalence of amyopathic patients developing fully-fledged DM (74), such an approach does not appear to be justified.

Treatment of interstitial lung disease associated with myositis

Myositis may be complicated in circa one third of cases by ILD, while sub-clinical ILD (defined as the presence of alterations on chest x-ray, HRCT of the lungs, or restrictive ventilatory defect regardless of respiratory symptoms) has been described in 65% of myositis patients (75). In particular, ILD occurs in 50-80% of patients with anti-synthetase antibodies (including anti-Jo-1) (76).

However, once ILD has developed, the presence of anti-Jo-1 antibodies does not appear to have a prognostic value for the outcome of ILD (77). The commonest pattern of myositis-associated ILD (81% of patients with PM and DM in a retrospective series) is of nonspecific interstitial pneumonia, but there are reports of bronchiolitis obliterans organizing pneumonia (also known as cryptogenic organizing pneumonia), diffuse alveolar damage, and usual interstitial pneumonia as well (78, 79). Most patients with the anti-synthetase syndrome require aggressive and often long-term immunosuppressive treatment for their condition (80). Various regimens have been proposed for induction and for maintenance treatment, although comparisons across studies are hampered by the small number of patients enrolled and by the relative heterogeneity of patients' characteristics. A common regimen is a combination of pulse cyclophosphamide therapy and high-dose GC followed by maintenance treatment with azathioprine (81) or other immunosuppressant medications such as methotrexate or cyclosporine (81, 82) usually in combination with low-dose GC. The evidence in favor of such a scheme has been provided by a RCT that showed superior efficacy of combined (oral cyclophosphamide and GC) therapy versus GC alone both in terms of clinical improvement and survival at three years (83). However, today pulse, rather than oral, cyclophosphamide therapy may be preferred because a RCT reported lower toxicity in the pulse compared with the oral cyclophosphamide group in terms of rate of leukopenia and severe infections as well as gonadal toxicity (84). The efficacy of cyclophosphamide in ILD patients has been confirmed in subsequent trials on patients with ILD both with and without myositis. In an open study, intravenous cyclophosphamide (0.5 g/m² every three weeks associated with prednisone 50 mg daily tapered over 6 to 8 weeks to 5-7.5 mg daily) was able to prevent worsening of ILD in all patients with a progressive disease course (81). HRCT scan of the lung showed resolution of ground glass opacities, while diffusion capacity for carbon monoxide (DLCO)

improved in two patients and normalized in three. Similarly, in another trial, intravenous cyclophosphamide (300-800 mg/m² given monthly at least six times) associated with oral prednisone (0.5-1 mg/kg/day for two weeks and subsequently tapered to a maintenance dose) led to an improvement of dyspnea in eleven out of seventeen patients with ILD and myositis (82). Eight patients had an at least 10% improvement of vital capacity, while a significant reduction in the HRCT score was achieved in nine patients. Early initiation of cyclophosphamide treatment has been linked to a better response in one (85) but not in another study (86).

A number of other agents have investigated for efficacy in treating ILD. In a retrospective review cyclosporine, variably combined with GC and other immunosuppressants, was effective in four out of ten cases of refractory, rapidly progressive ILD associated with DM or PM (87). Likewise, a survey of Japanese physicians with a special interest in the treatment of connective tissue diseases (CTD) revealed effectiveness of cyclosporine and GC therapy in 72% of myositis-associated acute ILD (88). Tacrolimus (0.075 mg/kg/day) has also been reported to improve or stabilize ILD in thirteen patients (6 with DM, 6 with PM, and one with undifferentiated CTD) with the anti-synthetase syndrome after an average of forty weeks (89). Another study reported that tacrolimus was markedly effective in achieving subjective, laboratory and radiographic improvement in two patients with myositis-associated interstitial lung disease (90). Azathioprine has been formally tested in a RCT comparing the active drug (3 mg/kg/day, not exceeding 200 mg daily) and prednisone with placebo and prednisone (91). Changes in lung function tests at one year were better, although not significantly, in the azathioprine arm, while survival analysis disclosed that 43% patients treated with azathioprine died during the nine-period follow-up year compared with 77% randomized to placebo. Finally, in a retrospective observational study on twenty-eight patients (five of whom with myositis) with ILD, MMF (1g twice daily) improved (nine patients) or

at least stabilized pulmonary function parameters, while the mean dosage of prednisone could be significantly decreased from 15 to 10 mg daily (92).

Treatment of myositis associated with connective tissue diseases

Most cases of myositis associated with CTD show fairly non-specific histological features of an inflammatory infiltrate without the typical features of DM or PM (6). In terms of disease severity, no difference between isolated and CTD-associated myositis has been reported, although patients with anti-RNP antibodies may have somehow milder histological changes (93). Therefore, patients with CTD and clinical myositis should be treated just as aggressively as patients with isolated myositis.

Treatment of myositis associated with the human immunodeficiency virus (HIV) infection

Muscle complaints are not infrequent in HIV patients, but HIV-associated myositis proper seems to occur relatively infrequently. Recently, Johnson *et al.* addressed this issue by studying patients attending an outpatient HIV clinic referred for raised CK levels or muscle weakness (94). They found that 13 out of the 64 (20%) patients attending the outpatient HIV clinic had biopsy-proven myositis (94). There was no correlation of severity of weakness, stage of HIV infection, or retroviral treatment with the CK level at diagnosis. Four patients had a spontaneous resolution of their myositis without treatment, while in the remaining patients a remission could be achieved with GC, methotrexate, azathioprine, or IVIG. The results of this study suggest that HIV-associated myositis has a relatively good prognosis and that treatment should be tailored accordingly.

Monitoring response to treatment in myositis patients

As better and more powerful agents become available for the treatment of inflammatory rheumatic diseases, there is a sharpened need for reliable tools to monitor disease activity and response to treatment. With specific regard to myositis, a consensus conference of

the International Myositis Assessment and Clinical Studies Group (IMACS) has proposed a core set of disease activity measures consisting of five domains: physician and patient global assessments of disease activity; muscle strength; physical function; serum activity of muscle enzymes; and an assessment tool to capture extra-skeletal muscle disease activity (95). The committee of the consensus conference has also proposed as possible candidates for a core set of measures to assess damage in myositis (defined as changes that persist for at least six months despite prior therapy) the following tools: physician global damage assessment, the use of the Health Assessment Questionnaire, an assessment of the severity of damage of different organ systems using visual analog scales, and a modification of the Systemic Lupus International Collaborative Clinics – American College of Rheumatology damage index (95). Finally, the IMACS has published consensus guidelines for defining disease improvement and worsening (96). In particular, improvement has been defined as an at least 20% improvement in three of any six core set measures (physician's global activity assessment, patient's global activity assessment, muscle strength, physical function, muscle-associated enzymes, and extramuscular activity assessment), with no more than two worsening by 25% or more (measures that worsen cannot include manual muscle strength) (96, 97). Criteria for disease worsening include a 20% or more worsening of the patient's global condition as assessed by a physician, a 20% or more worsening of global extramuscular organ disease activity, and worsening of 30% or more of any three of six IMACS core set activity measure (96). The IMACS has recommended that these criteria be used in future trials of adult and juvenile DM and PM. The ESR may be raised in active myositis (98), but is not a reliable marker of disease activity (34) and is thus inadequate for monitoring response to treatment. By contrast, muscle enzymes including CK and aldolase, which are released in active myositis by damaged muscles into the circulation, correlate better with disease activity, although

they may sometimes remain stubbornly low in spite of active disease or, conversely, moderately elevated in inactive disease, perhaps reflecting chronic muscle damage (99, 33, 26).

Quantitative assessment of muscle strength is the main outcome measure in the assessment of myositis patients. Isometric MMT is usually performed according to the extended (*i.e.*, allowing intermediate points) scale of the Medical Research Council ranging from 0 (complete absence of muscle activity) to 5 (normal muscle strength) (100). Change in muscle strength as measured by MMT is probably the commonest outcome measure in myositis trials, but serves also well in clinical practice to monitor disease activity and response to therapy. Whether performed using a dynamometer (101, 102) or manually by the examiner (personal observations) MMT has a good inter-observer reproducibility. On the downside, MMT is not able to discriminate between active and inactive disease, although sequential changes over time can be used to monitor disease activity (103).

Isometric tests, including MMT, assess largely type II (fast-twitch) muscle fiber activity, which is mostly responsible for high-intensity, short-term performance. However, it has been contended that type I (slow-twitch) muscle fiber activity should also be tested, since it is mostly responsible for endurance and thus is more representative of daily activities such as walking (104). Based on this concept, isotonic tests of proximal muscle function (*i.e.*, tests assessing type I muscle fiber activity) have been proposed as a useful adjunct to standard MMT assessment. These tests have shown in a preliminary study excellent test-retest reliability, as well as construct validity in respect to sensitivity to change in the inflammatory myopathies (104). On a similar note, a functional index and a modified version (functional index-2) developed specifically to evaluate muscle endurance in myositis patients have been shown to reliably discriminate patients from controls and to have high interrater reliability (105, 106). In a large RCT demonstrating the efficacy of creatine supplementation in myositis patients co-authored by one

of us (NP), the benefit conferred by the treatment could be captured both by standard MMT and by the functional index, suggesting that this treatment could improve muscle strength as well as muscle endurance (68). Other observations, however, have shown a poor correlation between muscle endurance and muscle strength tests, with the former showing a persistently poor performance despite improvement in the latter, suggesting that muscle strength and endurance may not be strictly coupled (107). Since MMT has been more extensively used in clinical trials, we feel that for the time being it is prudent to rely mainly on classical MMT to evaluate how myositis patients respond to treatment, but that assessment of muscle endurance *e.g.* using the functional index-index-2 should also become part of the assessment of myositis patients.

Needle EMG is useful mainly in diagnosis myositis. In active myositis, EMG usually shows increased spontaneous activity with fibrillations, complex repetitive discharges, positive sharp waves, and small polyphasic motor unit potentials (98, 33). The presence of spontaneous activity can help to distinguish active disease from GC-induced myopathy during the course of the disease, but these signs may be subtle or absent (33).

MRI is probably the best imaging technique available for the visualization of striated muscles (66). In active disease, fat-suppressed weighted images can show inflammatory muscle edema, while in chronic disease T1 weighted images are useful to document muscle atrophy and fatty infiltration (108). Theoretically, MRI could be used to document disease activity, to differentiate disease activity from chronic damage, and to monitor response to therapy (109, 110) but its use remains to be properly validated in adequately powered prospective studies (98). Discrepancies between MRI assessment of disease activity and assessment by other tools including muscle enzymes and histological findings have been reported (111). In selected, uncertain cases, histology can be a "last resort" to determine whether myositis is active, and to differentiate ongoing inflamma-

tion from disease-induced damage and steroid myopathy.

With regard to ILD, standard chest x-rays have been shown not to be able to accurately demonstrate the presence and extent of pulmonary involvement (112). By contrast, HRCT scan of the lungs (showing diseased anatomy) and pulmonary function tests, particularly DLCO (reflecting objective measures of function) strongly correlate in demonstrating interstitial lung disease and in monitoring response to treatment (113, 114). HRCT scan of the lungs should be performed at baseline when ILD is suspected but because of its heavy radiation exposure should not be repeated too frequently, whereas pulmonary function tests lend themselves well to serial measurements.

Conclusions

There is evidence that in spite of the available treatments, approximately one third of myositis patients are left with mild to severe disability (33). In addition, some patients may incur disability at least partially as a consequence of the treatment itself, particularly GC-induced myopathy. It is thus important to tailor the treatment to the individual patient – that is, to avoid both over- and under-treating – by early assessment of disease severity and by closely monitoring the response to therapy. A constant co-operation between Clinicians, Pathologists, Physiotherapists and, whenever required, other Specialists, including Chest Physicians, is also crucial in optimizing treatment. With the growing number of medications available for use, today's challenge is not simply to generate more and more drugs, but also to know how to use most effectively those that are at hand.

Acknowledgments

The Authors wish to cordially thank Prof. Timothy McAlindon, Division of Rheumatology, Tufts University School of Medicine, US, for kindly providing us with the full text of a case report submitted to the 2007 Eular meeting and Dr. Florenzo Iannone, Rheumatology Unit, University of Bari, Italy, for his friendly help in retrieving some references quoted in this paper.

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