The idiopathic inflammatory myopathies encompass especially two major and distinct subsets that are polymyositis (PM) and dermatomyositis (DM) [1–12]. PM and DM are systemic inflammatory disorders affecting the skeletal muscles, the skin and other organs [1–12]. The criteria for diagnosis of PM/DM are based upon Bohan and Peter [13,14]: symmetric proximal muscle weakness; increased serum muscle enzymes; myopathic changes on electromyography; typical histologic findings on muscle biopsy; and characteristic dermatologic manifestations in DM such as: heliotrope rash which is violaceous, with or without edema in a symmetrical distribution involving periorbital skin; and Gottron’s papules which are found covering prominence lesions. The causes of PM and DM is still unclear, although an autoimmune process is markedly implicated. In PM, CD8 cytotoxic T cells form immunologically synapses with the healthy muscle fibers they invade, resulting in muscle necrosis via the perforin pathway [15–17]. In DM, early activation of the complement cascade leads to both formation and deposition of membranolytic attack complex on the endomysial capillaries, leading to their destruction and muscle ischemia [18,19]. Although this physiopathogenic knowledge of PM/DM has strengthened the prospects for semi-specific immunotherapeutic agents, as discussed later, it is not sufficient for the...
application of specific immunotherapy because the antigens remain unknown in PM/DM. Consequently, to date, therapy of PM/DM is not selectively targeting the relevant: pathogenic autoreactive T cells in PM; and the complement-mediated process on the endomyzial capillaries in DM. Nevertheless, the non-specific immunotherapeutic drugs have markedly improved both short-term and long-term outcome of PM/DM patients.

Indeed, in the presteroid era, the prognosis of PM/DM was extremely poor. In the first literature review in 1903, Steiner et al. [20], in fact, described 17 deaths out of 28 cases of PM/DM (60.7%), indicating a very poor prognosis for the untreated patients; the remaining patients exhibited major disability related to muscle weakness. In 1940, an additional report also highlighted a 50% mortality rate in the untreated PM/DM patients [21]. After the introduction of steroids in the 1950s, 12 studies examined the mortality of PM/DM patients which ranged between 11 to 45% [9,11,22–28]. To date, PM and DM are still considered to be associated with morbidity and mortality rates, primarily related to life-threatening muscle weakness, cardiac, lung and esophageal impairment [3–12].

Because PM/DM are uncommon conditions with a prevalence of 11 per 100,000, it is difficult to study these orphan diseases in a randomized controlled fashion. In essence, until now, there have been very few randomized controlled series assessing the optimal therapy for PM/DM, and those that have been completed included limited samples of patients. In 2005, a Cochrane review article looking at randomized controlled studies, in fact, identified only five trials addressing PM/DM and none of these series dealt with long-term follow-up of patients [29]. Taken together, most studies regarding PM/DM therapy are retrospective.

Steroid therapy

Oral prednisone

Corticosteroids remain the first-line therapy of choice in PM/DM patients, although their efficacy has not been tested in randomized controlled trials: steroids versus placebo. Nevertheless, there is a strong clinical consensus that steroids improve PM/DM significantly in a great number of PM/DM patients [3,18,30–34]. Indeed, in retrospective series, 60 to 70% of PM/DM patients have been found to respond to oral prednisone and to achieve a complete or worthwhile remission [9,23,28,35–38]. The mechanisms of action of prednisone are still unclear in PM/DM, although many hypotheses have been postulated; indeed, prednisone is thought to exert a beneficial effect by: inhibiting recruitment and migration of lymphocytes to the areas of inflammation; and interfering with the synthesis of lymphokines, especially interleukin 1, interleukin 2 and tumor necrosis factor which are secreted by both activated macrophages and T cells [18].

Although different prednisone regimens have been mentioned, high-dose prednisone at an initial dosage of 1 mg/kg/day is considered to be the mainstay of therapy for PM/DM patients [3,9,30–34]. Most authors have recommended that prednisone should be given as a single morning dose; in essence, this single morning dose is less likely to inhibit the evening synthesis of adrenocorticotropic hormone, which results in a normal endogenous cortisol secretion the next morning [18]. Moreover, a higher morning concentration of prednisone therapy (i.e.: 1 mg/kg/day) is considered to lead to a better clinical outcome in PM/DM patients [18]. Prednisone is more efficacious than prednisolone in PM/DM; in a double-blind, randomized, cross-over study including healthy volunteers, Etienne et al. [39] mentioned both higher and earlier serum plasma prednisolone concentration after the administration of a single oral dose of prednisone compared with prednisolone.

After PM/DM has become clinically and enzymatically (that is decreased creatine phosphokinase [CK] level) inactive, usually after at least 4 to 8 weeks, the daily dose of prednisone can be tapered slowly, until the lowest possible dose controlling the myositis is reached [40,41]. The rate of prednisone tapering should not be too rapid, averaging less than 10 mg monthly, and it should always take into account patients’ clinical improvement [40,41]. The American College of Rheumatology did not address specific taper levels or the issue of maintenance doses, and the above-mentioned guidelines are, in fact, based on findings from case series and reports. Indeed, Oddis and Medsger [41] have examined the effects of different steroid regimens in PM/DM patients. If prednisone therapy is started at 1 mg/kg/day for at least 4 to 6 weeks after muscle strength improved and CK level is normalized, and then tapered at a rate of 10 mg/month, both favorable clinical and biochemical outcomes were achieved in up to 81% of PM/DM patients [41]. In contrast, if this prednisone regimen was not followed, only 48% of PM/DM patients exhibited good clinical and biochemical response [41].

Interestingly, PM/DM patients continue to exhibit mild or moderate increase of CK levels in the face of normal/stable muscle strength, and they should not receive continued or additional therapy based solely on CK level elevation [18]. Indeed, the major adverse events of long-term steroid therapy are encountered in as high as 32 to 41% of steroid-treated PM/DM patients [9,42]. In a long-term study of 77 PM/DM patients, steroid-related severe disability was observed in 14.3% of

Glossary

- CK: creatine phosphokinase
- DM: dermatomyositis
- PM: polymyositis
cases, resulting in: marked muscle weakness (n = 11), osteoporotic vertebral fracture (n = 3) as well as avascular necrosis of the femoral head (n = 1) [9].

**Pulsed intravenous methylprednisolone**

Pulsed intravenous methylprednisolone therapy was firstly used by Bohan [43] in an attempt to decrease steroid-related adverse events.

To date, pulsed intravenous methylprednisolone therapy, at a dose of 1 g/kg/day for 3 days and then switched to the oral prednisone regimen, is considered to be useful in patients with acute severe PM/DM or with PM/DM-related life-threatening extramuscular manifestations (e.g.: myocarditis, esophageal involvement), without evidence from randomized controlled trials [18].

Indeed, until now, only one open study has compared methylprednisolone pulses (500 mg/day for three consecutive days once a week for 3 to 9 weeks) plus oral prednisone (1 mg/kg/day) in 11 patients (eight PM, three DM) to oral prednisone (1 mg/kg/day) alone in 14 other patients (ten PM, four DM) [44]. The authors have observed that the rate of complete remission was higher in the methylprednisolone-treated group (90.9% vs. 42.9%), in which the CK level returned to normal more rapidly; moreover, deterioration of myositis tended to be more frequent in the prednisone-treated group (14.3% vs. 0%), although not significantly so [44]. However, no definite conclusion can be drawn from these preliminary results, and further investigations are warranted to confirm pulsed intravenous methylprednisolone therapy indications in PM/DM.

Finally, many factors have been reported to be associated with a reduced response to steroid therapy in PM/DM, especially:

- a prolonged duration of PM/DM symptoms before initiation of therapy. Interestingly, previous authors have mentioned that steroid efficacy is better in the group of PM/DM patients who received therapy at an early stage (i.e. within the first year following the onset of first muscle symptoms) compared with those without (48–57% vs. 0–47%) [9]. In another series, 34% of patients who started prednisone within 3 months after the onset of muscle symptoms showed resolution of myositis, whereas no patient had a complete response to prednisone when steroids were started more than 18 months after muscle signs’ onset [37];
- elderly patients [9,11];
- severe organ involvement, especially interstitial lung disease and cardiac involvement [38];
- an associated malignancy [9,11];
- and the presence of myositis-specific autoantibodies: anti-Jo1 antibody, anti-SRP antibody [6,9,38,42].

Overall, although many PM/DM patients have at least a partial response to steroid therapy, approximately 20–30% of PM/DM patients will not respond to prednisone therapy; indeed, if by the time (approximately 12 weeks after initiating prednisone therapy), there is no objective benefit (defined as increased muscle strength and no lowering of CK levels), patients should be considered unresponsive to prednisone [9,18,30–34]. Moreover, 30 to 50% additional PM/DM patients will develop significant steroid-related side effects [9,18,30–34]; in these patients, immunosuppressive drugs in the line of preference should be started.

**Additional therapy in dermatomyositis patients**

All patients exhibiting DM-related skin lesions should benefit from aggressive sun protection, using broad-spectrum sunscreen with a high sun protective factor [30]. Furthermore, hydroxychloroquine is currently used in treating cutaneous manifestations related to DM, especially peri-orbital heliotrope rash, facial erythema and periangual telangiectasias. Previous investigators have found that hydroxychloroquine, in dosages of 200 to 400 mg per day, resulted in complete healing of DM-related cutaneous involvement in up to 80% of patients [3,30,40,45–47]. Woo et al. [47] treated seven DM patients with refractory skin manifestations with hydroxychloroquine; in all patients, the skin lesions improved, disappearing entirely in three patients. Moreover, other authors have recommended that patients who do not respond well to hydroxychloroquine may be switched successfully to chloroquine phosphate at a dose of 250 to 500 mg per day [30].

Finally, the management of cutaneous calcinosis still remains difficult in PM/DM patients. In case reports, different drugs have been used with diverging results to treat cutaneous calcinosis, i.e.: diltiazem, colchicine, probenecid, low-dose warfarin, alendronate or pamidronate [3,30,48–52]. However, to date, none of these drugs has proven to be effective in DM patients with calcinosis cutis. In few DM patients, surgical excision may be useful for larger deposits that are particularly symptomatic [33].

**First-line immunosuppressive therapy**

To date, in PM/DM patients, the decision to start with an immunosuppressive therapy is based on the following parameters [18]: an appropriate dose of prednisone for at least 2 to 3 months has been ineffective; attempts to lower a high steroid regimen have recurrently resulted in PM/DM relapses; and need for immunosuppressive therapy “steroid-sparing” effect, when despite steroid responsiveness, the patient develop serious steroid-related side effects. However, once again, immunosuppressive therapy use is based more commonly on clinical experience rather than on findings of randomized controlled trials.

Therefore, the preference for selecting the first-line immunosuppressive agent still remains empiric in PM/DM and is more often based on personal experience with each drug and its
relative efficacy-safety ratio. In clinical practice, the two major drugs used in the treatment of steroid-resistant PM/DM are methotrexate and azathioprine.

Azathioprine

Azathioprine, a derivative of 6-mercaptopurine agent, is used in steroid-refractory PM/DM. Azathioprine is usually administered orally at a dose of 2–3 mg/kg daily. Increase of liver enzymes is the main toxic effect in azathioprine-treated patients [9].

Azathioprine efficacy in PM/DM is mainly supported by a small number of case reports [9,53–55]. In a small series, 12% of PM/DM patients responded completely to azathioprine, 52% responded partially and 36% did not improve at all [56]. In other retrospective studies, 57 to 75% of azathioprine-treated PM/DM patients exhibited improvement of myositis [9,55,57]. To date, a single double-blind randomized study has, in fact, been conducted with azathioprine (2 mg/kg/day) plus prednisone (60 mg/day) compared to prednisone alone (60 mg/day) in 16 patients with PM/DM [58]. After 3 months of therapy, muscle strength ($P = 0.58$), CK level ($P = 0.21$) and muscle histological damage ($P = 0.8$) did not differ between the azathioprine ($n = 8$) and the placebo ($n = 8$) groups (table 1) [53]. However, this follow-up period of 3 months was likely too short to detect a statistically significant improvement in muscle function; Dalakas [18] has, in fact, underlined that if effective the azathioprine muscle effects are observed after 6 to 8 months. Therefore, patience is required before it is concluded that azathioprine is ineffective in PM/DM. Indeed, a subsequent open study re-evaluation of the same steroid and azathioprine patients showed that the combination of azathioprine and prednisone was better than prednisone alone at 3-year follow-up; azathioprine-treated patients exhibited a better functional muscle status and still received lower daily doses of prednisone [53].

Methotrexate

The use of methotrexate, an antagonist of folate metabolism, was first reported in steroid-refractory PM in 1968 [59]. Subsequently, a few case reports and retrospective reviews have also suggested that methotrexate may be effective in PM/DM [37,55,60–69]. Firstly, Bohan et al. [23] treated 25 patients with steroid-resistant PM/DM with methotrexate; 88% of these latter patients exhibited a significant PM/DM improvement and 43% of patients were able to reduce their steroid daily dose. In other rheumatologic retrospective series, overall response rates to methotrexate have ranged from 50 to 77% in PM/DM patients.

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AZA: azathioprine; MTX: methotrexate; IV Ig: intravenous immunoglobulins.
methylmethotrexate was used in different ways: orally, subcutaneously or intramuscularly; it was administered up to a total dose of 25 mg weekly [range: 15–25 mg/week]. The main side effects of methotrexate are gastrointestinal symptoms, liver and bone marrow toxicity; another side effect is methotrexate-related hypersensitivity pneumonitis, which can be difficult to distinguish from PM/DM-associated interstitial lung disease [18]. Two other dermatologic retrospective series have further indicated that cutaneous manifestations of DM responded well to methotrexate, with improvement of clinical signs in all patients [62,68]. Nevertheless, until now, there has never been a randomized controlled trial comparing the use of both methotrexate and oral prednisone.

Only few studies have evaluated the comparative efficacy of methotrexate and azathioprine [37,56,69]. In a double-blind comparative series of methotrexate and azathio- prine, the two drugs had similar efficacy in PM/DM patients (n = 28); indeed, the rates of improvement (72.8% vs. 63.7%) and deterioration (27.2% vs. 36.3%) did not differ between methotrexate- and azathioprine-treated patients, but methotrexate was better tolerated (table I) [56]. Interestingly, other authors observed that PM/DM patients with antisyntetase syndrome tended to exhibit a better response to methotrexate than to azathioprine, although not significantly so [37].

Finally, previous investigators have underscored that methotrexate has the advantage to act faster than azathioprine with muscle results expected within 6 to 8 weeks after therapy initiation [18]. Although methotrexate appears to be a reasonable choice in patients with steroid-resistant PM/DM, it is unclear whether it would be helpful when used as initial treatment.

Combined therapy of azathioprine and methotrexate

In PM/DM patients who failed to respond to methotrexate or azathioprine alone, the combination of azathioprine and methotrexate has been recommended by few authors [34,67]. To date, a sole randomized cross-over study compared the effect of weekly oral methotrexate (25 mg) and daily oral azathioprine (150 mg) with that of intravenous methotrexate (25 mg/week) in 30 PM/DM patients [67]. At 6-month follow-up, of the 15 patients initially randomized to oral methotrexate-azathioprine, 12 (80%) had improved muscle strength; on the other hand, only four of the 15 patients (26.7%) exhibited improvement of myositis with intravenous methotrexate (table I). Consequently, the oral combination methotrexate-azathioprine was found to be effective in many patients who failed to respond to either drug alone [67]. These latter findings suggest that combined therapy of azathioprine and methotrexate may be helpful in treating refractory myositis before choosing more cytotoxic regimens.

Second-line therapy in patients with refractory polymyositis/dermatomyositis

Intravenous immunoglobulins

Intravenous immunoglobulins have multiple mechanisms of actions, including: inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor of macrophages or the immunoglobulins on B cells, blocking the Fc receptors on target antigens, and interference with antigen recognition by sensitized T cells [18]. To date, intravenous immunoglobulin therapy is recommended in patients exhibiting PM/DM refractory to: steroids, methotrexate or azathioprine [70]. In the first pilot open series [71], PM/DM patients were given intravenous immunoglobulin therapy at a dose of 1 g/kg/day for 2 days monthly; intravenous immunoglobulin therapy resulted in increased proximal muscle strength and reduction in the CK level. In other open studies, intravenous immunoglobulins have also been used successfully in as high as 67 to 92% of patients with refractory myositis [9,72–77]. Interestingly, in a double-blind placebo-controlled study, Dalakas et al. [78] assessed the efficacy of high-dose intravenous immunoglobulin infusions in 15 patients with steroid-resistant DM. Patients were randomly assigned to receive either 2 g/kg of intravenous immunoglobulins (n = 8) or placebo (n = 7) monthly for 3 months. Intravenous immunoglobulin-treated patients exhibited a statistically significant improvement in muscle strength (100% vs. 42.9%) and muscle symptoms (P < 0.035) (table I); the muscle strength improvement became rapidly noticeable (about 15 days after the first infusion), and it was clear after the second infusion [78]. Furthermore, these authors also found a marked improvement in the active skin lesions of DM in the intravenous immunoglobulin-treated group [78]. Finally, muscle histology in the intravenous immunoglobulin-treated patients showed a significant improvement, including: an increase in muscle fiber diameter; and increased capillary number and decrease in the diameter of capillaries, as well as reduced complement deposits (especially C3b and the membrane attack complex) on capillaries [78]. In addition, many authors have suggested that repeated infusions of intravenous immunoglobulins may be required every 6 to 12 weeks to maintain improvement in some PM/DM patients [18].

Furthermore, intravenous immunoglobulin therapy is also recommended in patients who are unable to continue immunosuppressive agents because of adverse effects, as well as in patients in whom such agents are contraindicated [9,18,77,79]. Interestingly, other authors have recently mentioned that intravenous immunoglobulin therapy should be considered in life-threatening esophageal impairment complicating PM/DM [80]. Indeed, in a retrospective study, 73 patients with steroid-refractory esophageal involvement related to PM/DM received IV Ig therapy (2 g/kg, monthly); 25 of these patients exhibited
life-threatening esophageal complications requiring exclusive enteral feeding and 33 patients developed aspiration pneumonia related to esophageal dysfunction [80]. Sixty of the intravenous immunoglobulin-treated patients exhibited dramatic and rapid resolution of esophageal clinical manifestations (82.2%), leading to return to normal oral feeding and ablation of feeding enteral tubes, and four other patients improved (5.5%) [80]. In these patients, esophageal symptom improvement became noticeable within 15 days after the first intravenous immunoglobulin infusion, and became clear after the second infusion. These authors have further suggested that combined therapy of intravenous immunoglobulins and high-dose steroids may be the first-line therapy in PM/DM patients with life-threatening esophageal manifestations [80].

**Cyclosporine**

Cyclosporine is a T cell immunosuppressant; it inhibits transcription of certain genes, especially the interleukin 2 gene, leading to reduced IL2 and other cytokines [18].

Previous authors have found that cyclosporine may be a useful therapy in patients with refractory PM/DM [81–86]. Firstly, Bendtzen et al. [87] reported the use of cyclosporine in PM/DM. Other case reports and small open series have suggested that cyclosporine may be efficacious in 50 to 70% of PM/DM patients at a dose up to 150 mg twice daily [18,30,33,34,82,84,86,88–92].

A single randomized study compared the efficacy of methotrexate with cyclosporine therapy [93]. Thirty-six patients with refractory active PM/DM (20 DM, 16 PM) were randomized to receive either methotrexate at a dose of 7.5–15 mg/week ($n = 17$) or cyclosporine at a dose of 3–3.5 mg/kg/day ($n = 19$) in addition to prednisone. During the 6-month follow-up period, methotrexate and cyclosporine did not differ significantly in their effect in PM/DM regarding improvement of muscle strength and decrease of CK levels; however, the group of methotrexate-treated patients exhibited a more rapid improvement of myositis at 1- and 3-month follow-up ($P < 0.05$) (table I) [93].

Finally, cyclosporine may be useful in steroid-resistant interstitial lung disease related to PM/DM at a dose of 5–7.5 mg/kg/day [6,8,94–101]. Maeda et al. [102] treated three patients with PM/DM and interstitial lung disease with cyclosporine, and none died of respiratory failure. In Kobayashi et al.’s [95] series, cyclosporine was effective in three of five PM/DM patients with steroid-resistant interstitial lung disease. Nevertheless, cyclosporine therapy necessitates monitoring during the first few months to ensure its trough serum level is optimal (100–200 mg/mL) [31]. Furthermore, cyclosporine is toxic to many organs, i.e.: the kidneys, liver and bone marrow. Consequently, renal tests should be closely monitored in PM/DM patients; when creatinine levels increase more than 30%, cyclosporine should be discontinued. Indeed, in Vencovsky et al.’s [93] series, six of the 19 PM/DM patients developed cyclosporine-associated adverse effects; cyclosporine had to be withdrawn definitively in up to three of these six latter patients. Taken together, in current practice, because cyclosporine use is difficult, this drug may be reserved for PM/DM patients who have failed to respond adequately to steroids, other immunosuppressive agents and intravenous immunoglobulins.

**Cyclophosphamide**

Cyclophosphamide, an alkylating agent, has also been used to treat PM/DM patients. However, the efficacy of cyclophosphamide in PM/DM is very controversial as regards case reports and open series’ results [103–106]. In 1989, in a retrospective study, 11 patients with steroid-refractory PM/DM were given intermittent intravenous pulsed cyclophosphamide (0.75–1.36 g/m² monthly) [105]. The authors found that only 14.3% of cyclophosphamide-treated patients met defined criteria for improvement in muscle strength; moreover, serious infections occurred in as high as 18.2% of patients and 9.1% died from cyclophosphamide-related complications [105]. Adverse effects of cyclophosphamide include especially nausea/vomiting, alopecia, hemorrhagic cystitis, bone marrow suppression and secondary malignancies [103–106]. Taken together, intravenous cyclophosphamide cannot be recommended for the treatment of patients with refractory active myositis.

To date, most authors have recommended that cyclophosphamide therapy should be restricted to PM/DM patients with interstitial lung disease [8–10,18,107]. In these latter patients, intravenous pulsed cyclophosphamide is more often used at a dose of 0.8 g/m² (range: 0.5–1 g/m²) monthly, although an oral regimen of 1.5 to 2 mg/kg/day might be preferred by some investigators [8,18,108–111]. A prospective trial of intravenous pulsed cyclophosphamide in interstitial lung disease-associated connective-tissue disease included two patients with PM; cyclophosphamide was administered at a dosage of 0.5 g/m² every 4 weeks for nine cycles; dyspnea improved and the ground glass opacities markedly regressed in these two PM patients [112]. In a retrospective study, intravenous pulsed cyclophosphamide monthly for six cycles was used in ten of 36 PM/DM patients with interstitial lung disease [8]. At 21 months follow-up, half of the cyclophosphamide-treated patients have either resolved ($n = 3$) or improved ($n = 2$) pulmonary status; interestingly, the authors have noted that cyclophosphamide was used at an earlier lung histologic stage in patients with improved pulmonary status [8]. In another retrospective series, cyclophosphamide (0.3 to 0.8 g/m² every 4 weeks for six cycles) was also used in 17 PM/DM patients with interstitial lung disease; at 7-month follow-up, dyspnea improved in 67% of patients, vital capacity improved significantly (> 10%) in 47% of cases [107]. More recently, ten other patients with DM...
and acute severe interstitial lung disease (i.e.: histologically proven diffuse alveolar damage) were given a combined therapy of prednisone, intravenous pulsed cyclophosphamide (10–30 mg/kg every 3 weeks) and cyclosporine (2–3 mg per day) [113]. The authors observed an improvement of prognosis in these patients with a 2-year survival rate of 50% [113]; indeed, in this group of patients, the survival rate has been previously found to be extremely poor, ranging from 0 to 25% [6,8]. Overall, Kameda et al. [113] suggested that such an aggressive immunosuppressive therapy may be useful in the group of patients with fulminant interstitial lung disease (that is diffuse alveolar damage), although no definite conclusion can be drawn from these data.

**Mycophenolate mofetil**

Mycophenolate mofetil is a morpholinoethylster of mycophenolic acid that blocks de novo purine synthesis and acts on both B and T cells [18]. Mycophenolate mofetil has been used to treat PM/DM patients in few small series and case reports, which suggested that this drug may help improvement of muscle strength, serum CK levels as well as cutaneous manifestations [114–120]. Mycophenolate mofetil was administered orally at a dose of up to 3 g per day taking up to 3 months to see the benefits of treatment [18].

A small case series examined four patients with refractory PM/DM; muscle strength increased in all patients and steroid requirement decreased concomitantly [118]. In our literature review of case reports or small trials, including four DM and seven PM with refractory myositis, we have observed that mycophenolate mofetil resulted in improved muscle strength in up to 91.7% of cases [114–120]. In another open study, 12 patients with refractory DM received mycophenolate mofetil; muscle strength and cutaneous manifestations improved in 83% of patients; nevertheless, the authors reported that two patients developed severe adverse effects related to mycophenolate mofetil, i.e.: B cell lymphoma (n = 1) and severe hepatitis (n = 1) [116].

Furthermore, an open trial of mycophenolate mofetil in 28 interstitial lung disease-associated connective-tissue disease included five patients with PM/DM who received mycophenolate mofetil at a dosage of 30 mg/kg/day; at 18-month follow-up, findings of pulmonary function tests, that are force vital capacity, DLCO had not improved significantly, although values were unchanged in most patients [121]. Taken together, mycophenolate mofetil efficacy in interstitial lung disease related to PM/DM remains to be proven.

To date, safety concerns have been recently raised in mycophenolate mofetil-treated PM/DM patients [121]. Indeed, in an open series of ten mycophenolate mofetil-treated DM patients, opportunistic infections have been reported in three patients, including one which proved fatal; in these three patients, opportunistic infections occurred within 5 to 6 months after initiation of mycophenolate mofetil [122,123].

**Leflunomide**

Leflunomide is an immunomodulatory drug that inhibits pyrimidine synthesis.

Leflunomide has been found to be effective in five patients (three DM, two PM) with refractory myositis [124,125]. Boswell et al. [124] have, in fact, reported three cases of recalcitrant cutaneous manifestations related to DM that responded to the addition of daily leflunomide (at a daily dose of 20 mg). As regards literature findings, further studies are necessary to evaluate the efficacy of leflunomide in PM/DM patients, as well as to determine the ratio safety-risk of leflunomide in PM/DM.

**Tacrolimus**

Tacrolimus binds the immunophilin FKBP12 and inhibits calcineurin, resulting in inhibition of T-cell signal transduction and IL2 transcription.

There is only anecdotal evidence that tacrolimus is effective in some difficult to treat PM/DM patients, especially in the subgroup with PM associated with interstitial lung disease and antisynthetase syndrome [126–128]. In a sole open study, eight patients with PM (six with anti-Jo1 antibody and two with anti-SRP), who failed to respond to multiple immunosuppressive agents, were given tacrolimus [126]. All tacrolimus-treated patients exhibited improvement of muscle strength, and five of the six anti-Jo1 patients regained normal muscle strength; the mean CK level of the six anti-Jo1 patients also decreased significantly (from 3114 to 87 IU/L; P < 0.1) [123]. Moreover, extravascular manifestations, that are fever, polyarthritis, “mechanic hands” and interstitial lung disease also improved [126]. Nevertheless, no definite conclusion can be drawn from these preliminary data.

**Plasma exchange**

Plasma exchange is used in the treatment of refractory autoimmune diseases, in order to remove circulating autoantibodies and immune complexes. Using plasma exchange has yielded divergent results with no benefit in a controlled study [129,130]. In an open study, the results of plasma exchange appeared promising in a limited sample of patients with refractory PM/DM [129]. However, in a randomized, double-blind controlled trial, Miller et al. [130] found that plasma exchange was not effective in patients with refractory PM/DM. Overall, given the absence of efficacy and the potential severe complications of plasmapheresis, such a therapy is not recommended in PM/DM patients. To date, further investigations are warranted to assess whether plasma exchange may be useful in certain subsets of patients, such as patients with anti-SRP antibody.
Biotherapies in patients with refractory polymyositis/dermatomyositis

In most patients who failed to respond to PM/DM therapy, it is crucial to have a critical look at the initial diagnosis. In such patients, most authors have strongly recommended to perform a new diagnostic muscle biopsy, in order to exclude underlying: inclusion body myositis, necrotizing myopathy as well as inflammatory muscular dystrophy (e.g.: dysferlinopathy, calpainopathy, caveolinopathy, sarcoglycanopathy). If the diagnosis of PM/DM is definitely reconfirmed by histological muscle biopsy findings, a number of agents may be empirically used in these patients.

TNF-α antagonists

Firstly, anecdotal reports have suggested that anti-TNF-α agents (i.e.: infliximab, etanercept, adalimumab) may be helpful in the therapy of patients with active refractory PM/DM. In our literature review, we have, in fact, found 18 case reports of patients with resistant myositis (ten DM, eight PM) who successfully took infliximab at a dose of 3–10 mg/kg/day; improvement of muscle strength was observed in 94.1% of patients [131–140]. Twenty-eight additional patients (12 DM, 16 PM) were given etanercept (25 mg twice weekly subcutaneously); muscle strength improved in only 39.3% of patients [133,138–141]. Nevertheless, more recent open-label studies demonstrate that anti-TNF-α agents clearly show no benefit in PM/DM [134,138,140]. In five DM patients who received etanercept therapy, the muscle weakness was either unchanged or deteriorated and the muscle enzyme levels increased concurrently [141]. In another study, six patients with refractory myositis (two PM, four DM) received infliximab at a dose of 10 mg/kg; at 26-week follow-up, 66% of patients exhibited a marked deterioration of both muscle strength and interstitial lung disease [134]. In an additional series, nine patients with refractory myositis (five PM, four DM) received four infusions of infliximab (5 mg/kg); the authors reported a deterioration of muscle strength in as high as 78% of cases; histological analysis of repeated muscle biopsy specimens also demonstrated a worsening of muscle damage [140]. Moreover, other investigators have underscored that TNF-α antagonists may induce the onset of autoimmune diseases [142]. Indeed, the onset of myositis has been highlighted in patients with rheumatoid arthritis during anti-TNF-α therapy [136,140,143]. Furthermore, Klein et al. [144] have described four cases of DM that developed or were exacerbated by exposure to the TNF-α antagonists: etanercept and adalimumab; the authors have speculated that the exacerbation of PM/DM might have been mediated by abnormal activation of the type I interferon pathway, which has been implicated in the pathogenesis of PM/DM [140,145].

Taken together, in view of previous authors’ results as regards anti-TNF-α therapy use in PM/DM, anti-TNF-α agents should not be recommended as an alternative treatment in patients with resistant myositis. Indeed, safety concerns have markedly been raised in anti-TNF-α-treated PM/DM patients [122]; a case of fatal Mycobacterium fortuitum pneumonia has been described previously in a DM patient [146].

Interleukin 1 receptor antagonist

The interleukin 1 antagonist anakinra has been found to be effective in a sole patient with antisynthetase syndrome, resulting in improvement of muscle strength as well as in other extramuscular manifestations of PM/DM (i.e.: fever, polyarthritis) [147].

A multicenter, controlled trial of interleukin 1 antagonist in PM/DM patients with refractory myositis is underway.

Rituximab

Rituximab is a monoclonal antibody against CD 20 B cells that results in B cell depletion for at least 6 months [18]. On the basis of a number of case reports’ data, rituximab may be effective in PM/DM patients who are resistant to other therapies [148–156]. However, until now, there are no specific guidelines as regards the optimal rituximab regimen to use in PM/DM patients, i.e.: rituximab at either 375 mg/m² weekly for 4 weeks or at least 1 g in each of two biweekly infusions (total of 2 g).

In our literature review, we have found 19 case reports of PM/DM patients (ten DM, three PM, two antisynthetase syndromes) who were given rituximab for steroid-refractory myositis with favorable outcome; four of these patients exhibited a relapse of myositis at 8- to 10-month follow-up [149–155,157–159]. In an open pilot trial, eight DM patients received rituximab, leading to increased muscle strength in six patients (75%); muscle weakness improved by at least 50% in three of these six latter patients [151]. In an additional open series, six patients with refractory DM received rituximab (375 mg/m²/week for 4 weeks) [160]. At 3-month follow-up, rituximab resulted in increased muscle strength from baseline by 36 to 113%; all patients also showed concomitantly decreased CK values [160]. Nevertheless, 66% of patients developed a relapse of DM at 52-month follow-up [160]. Finally, one multicenter, placebo-controlled trial of rituximab in PM/DM patients with refractory myositis is underway; a French multicenter phase II study of rituximab in patients with resistant myositis and anti-Jo1/anti-SRP antibody is also underway (NCT00774462).

Furthermore, few authors have mentioned that rituximab may be helpful in PM/DM-related interstitial lung disease [161]. In a pilot study, 11 patients with antisynthetase syndrome and interstitial lung disease received rituximab; at 6-month follow-up, pulmonary function tests showed a significant improvement of vital capacity (> 10%) and DLCO (> 15%) in
64% of cases; nevertheless, one of the 11 patients died of fulminant *Pneumocystis jiroveci* pneumonia 3 months after the initiation of rituximab therapy [161].

Finally, a case of progressive multifocal leukoencephalopathy has been described in a patient with PM treated with rituximab; in this patient, progressive multifocal leukoencephalopathy occurred 5 months after the third rituximab infusion [122]. These findings, in fact, underline the importance of increasing awareness of progressive multifocal leukoencephalopathy among physicians regarding the group of rituximab-treated PM/DM patients, so this may be an issue to consider before rituximab therapy initiation in PM/DM patients [122].

**Future drugs in patients with refractory polymyositis/dermatomyositis**

Drugs that target co-stimulation molecules such as the human lymphocyte membrane proteins LFA-1 and LFA-3 (e.g.: efalizumab and alefacept) could be of interest in PM/DM, provided the safety concerns regarding the occurrence of progressive multifocal leukoencephalopathy are resolved [18]. Daclizumab is an interleukin 2 receptor antagonist that targets the signalling pathways involved in T cell activation. Daclizumab could be useful to explore in the therapy of PM/DM [18]. Anti-T-cell signalling drugs such as alemtuzumab might also be helpful in PM/DM. To date, alemtuzumab has been shown to be effective in one single patient with refractory PM [162]. Eculizumab is a monoclonal antibody against the complement protein C5 that could be relevant to the treatment of DM, of which the main cause is a complement-mediated-microvascularopathy [18].

In addition, drugs that target B cell growth factors, such as BAFF and APRIL, could also have promise for the treatment of myositis [18]. Finally, anti-adhesion-molecule drugs affect transmigration of B cells or T cells across the endothelial cell wall. Natalizumab, the best-known agent of this category, may be a helpful drug to test in PM/DM.

**Rehabilitation measures**

PM/DM patients exhibit a loss of muscle mass, which can be induced by different mechanisms, i.e.: immune-mediated muscle fibre damage, physical inactivity or adverse effects of glucocorticoid therapy. Therefore, appropriate exercise therapy is an integral component of therapy in PM/DM patients; consequently, it should be initiated concomitantly with steroid and/or immunosuppressive agents. In fact, exercise therapy allows to: increase protein muscle synthesis, muscle strength, vascularization of myocytes; and decrease tendinous retraction [163–167].

To date, few studies have specifically evaluated the efficacy of exercise programs to improve muscle strength, endurance and cardiovascular fitness in PM/DM patients. Nevertheless, previous authors have recommended that the types of exercise that may be proposed in muscle strength training programs should include: isometric, isotonic and isokinetic (concentric and eccentric) exercise [163–168]. In a series of five patients with active PM/DM, an increased muscle strength was observed following a standardized program that included non-resisted exercise, manually resisted exercise, cycling and stepping [165]. In addition, 13 other patients with refractory active PM/DM were randomized to receive either a 6-week aerobic training program using a cycle ergometer (*n* = 8) or a non-specific exercise program (*n* = 5); at 6-week follow-up, patients who underwent the aerobic training program exhibited a statistically significant improvement of activity score (*P* < 0.02), effort isometric peak and VO2 max (*P* = 0.03) [167]. In another series, ten PM/DM patients exhibited a significant improvement in quality of life score (SF 36), exercise tolerance and expiratory peak flow findings after a 12-week aerobic training program [164]. Finally, a 6-week aerobic program using a cycle ergometer resulted in a significant improvement in aerobic capacity and exercise tolerance in PM/DM patients, and there was also an improvement in the isometric strength of the hip flexors and knee extendors and in a functional assessment scale [166].

Nevertheless, further research is required to determine the optimal training protocols, although both resisted strength training and aerobic training programs have proven to be of benefit to PM/DM patients and may assist in counteracting the effects of high-dose steroids. Therefore, improvement or maintenance of

<table>
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<td><strong>Therapeutic</strong></td>
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<tr>
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<tr>
<td>Methotrexate</td>
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<td>Azathioprine</td>
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<td>High-dose intravenous immunoglobulins</td>
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<tr>
<td>Ciclosporine</td>
<td>1</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Mycophenolate mofetil</td>
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<tr>
<td>Not plasmapheresis</td>
<td>1</td>
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muscle strength and endurance will have a positive effect on the ability of patients to be active and independent in daily life. In conclusion, because PM/DM are uncommon conditions, randomized placebo-controlled studies are rare in these patients (table 2). Our therapeutic approach begins with a high-dose regimen of oral prednisone (at an initial dose of 1 mg/kg/day), which is then tapered slowly based on patients’ clinical response. In patients with steroid-refractory PM/DM, we more often start with methotrexate, as methotrexate has the advantage to act faster than azathioprine with results expected within 8 weeks. If patients exhibit methotrexate refractory PM/DM, other agents are required, i.e.: azathioprine or intravenous immunoglobulins. In most patients who failed to respond to such PM/DM conventional therapy, it is crucial to have a critical look at the diagnosis. In such patients, we strongly recommend to perform a new diagnostic muscle biopsy, in order to exclude underlying: inclusion body myositis, necrotizing myopathy or inflammatory muscular dystrophy. If the diagnosis of PM/DM is definitely reconfirmed by histological muscle biopsy findings, a number of agents may be empirically used in these patients, such as mycophenolate mofetil or rituximab. To date, TNF-α antagonists should not be considered in PM/DM patients, as these agents have been shown to induce exacerbation of myositis and lead to an increased risk of severe pyogenic and opportunistic infections in PM/DM patients [5,122,142,169].

Conflicts of interests: none for this article.

References

Therapy of polymyositis and dermatomyositis


Theory of polymyositis and dermatomyositis


