Dermatomyositis and polymyositis: from immunopathology to immunotherapy (immunobiologics)

Samuel Katsuyuki Shinjo1, Fernando Henrique Carlos de Souza2, Julio Cesar Bertacini de Moraes2

ABSTRACT

Idiopathic inflammatory myopathies (IIM), which include dermatomyositis (DM) and polymyositis (PM), are chronic systemic diseases associated with high morbidity and functional disability. Current treatment is based on the use of glucocorticoids and immunosuppressive drugs, but a considerable number of patients is refractory to traditional therapy. That has led to the attempted use of biologics based on the physiopathogenesis of IIM. From the immunopathological viewpoint, PM and DM differ: the former is more related to cellular immunity, while the latter, to humoral immunity. In both, however, elevated concentrations of proinflammatory interleukins (TNF, IL-1, IL-6) and increased expression of molecules related to costimulation of T lymphocytes have been described; thus, the use of biologics in those conditions seems reasonable. Considering the biologics available, open-label studies are scarce, comprising mainly case reports and series. TNF blockers have yielded conflicting results, with no evidence of good response to treatment. The anti-CD20 therapy has the most promising results. Data on T lymphocyte costimulation blockade and anti-IL-6 therapy are extremely scarce, preventing any consideration. Thus, the use of biologics in IIM still remains an unconquered frontier. Biologics may have an important role in the management of IIM refractory to conventional therapy, but further prospective studies based on objective parameters of response to treatment are needed. So far, anti-CD20 therapy seems to be the most promising treatment for refractory IIM.

Keywords: dermatomyositis, polymyositis, biological therapy, immunotherapy.

© 2013 Elsevier Editora Ltda. All rights reserved.

INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are part of the idiopathic inflammatory myopathies (IIM), a heterogeneous group of chronic systemic autoimmune myopathies, associated with high morbidity and functional disability. Each has different epidemiological, histological, immunohistochemical, pathological, and clinical characteristics, as well as different disease courses.

Being uncommon diseases, drug therapy for DM and PM is mainly based on case reports or series. In general, corticosteroids have been recommended as first-line drugs, and, as corticosteroid-sparing agents, several immunosuppressive drugs. However, a significant number of patients do not respond satisfactorily to those traditional treatments. In such cases, biologics are used based on the physiopathology of DM and PM.

MATERIALS AND METHODS

A systematic review of the articles available in the literature was performed, including articles published up to January 2012. The review was based on a bibliographic search in the Medical Literature Analysis and Retrieval System online...
The following terms were assessed: dermatomyositis, biologics, immunobiologicals, immunopathology, polymyositis, drug therapy, and treatment.

**Immunopathology**

Polymerositis is characterized by an infiltrate of CD8+ T lymphocytes and macrophages in muscle fibers, which express increased MHC class I antigen levels and release perforin granules, resulting in lysis of the muscle fibers. In DM, B lymphocytes play a relevant role in the disease pathogenesis due to the presence of autoantibodies, the deposition of immune complexes in the dermal-epidermal junction of skin lesions, and the presence of B lymphocytes around inflamed muscle fibers and perivascular areas.

**Cytokines and chemokines**

Cytokines and chemokines produced by muscle fibers, and inflammatory and endothelial cells can contribute to the pathogenesis of myopathies. Proinflammatory cytokines, such as interleukins 1α (IL-1α) and IL-1β, tumor necrosis factor α (TNF-α), interferons α and β (IFN-α and INF-β), and high-mobility group protein B1 (HMGB1), in addition to chemokines (such as α-chemokines (CCL2, CCL3, CCL4, CCL19, CCL21)) and β chemokines (CCL2, CCL3, CCL4, CCL19, CCL21), are present in the muscle tissue of patients with DM and PM.

Other cytokines, such as IL-15 and IL-18, have been recently described, suggesting they might play a role in the pathogenesis and activity of myositis, requiring further studies.

The treatment of the myopathies refractory to conventional treatment might, at least theoretically, be targeted at blocking those cytokines and chemokines.

**Tumor necrosis factor**

The TNF has been correlated with the pathogenesis of IIM. Using immunohistochemistry and in situ hybridization, Kuru et al. have shown that muscle fibers of patients with DM and PM express and synthesize TNF, while Lundberg et al. have shown increased levels of messenger RNA (mRNA) of TNF in muscle biopsies. Shimizu et al. have found increased serum levels of soluble TNF receptors in DM and PM. The levels of other cytokines, such as TNF-β, IL-1α, IL-1β, IL-2 and IFN-γ, are also increased in muscle biopsies of patients with DM and PM, contributing to the local inflammation cascade.

It is worth noting that TNF, IL-1 and IFN induce the expression of MHC class I antigen by muscle fibers, and both regulate muscle metabolism and regeneration.

**Interleukin 1**

Muscle weakness has been suggested not to correlate with the presence of inflammatory cell infiltrates; however, the presence of IL-1 detected in endothelial cells of patients with muscle weakness and no inflammatory cell infiltrate suggests the participation of proinflammatory interleukins. TNF has catabolic effects and works together with IL-1, leading to skeletal muscle mass loss. The increased expression of IL-1 (IL-1α, IL-1β, IL-1Ra), on its turn, correlates with the increase in IL-1 receptor in muscle fibers, intensifying the immune mechanism of myositis.

IL-1α, which is markedly expressed in the muscle tissue of patients with myositis, can stimulate the production of prostaglandin E2 (PGE2) in skeletal muscle.

**Interleukin 6**

The serum levels of IL-6 are also elevated and correlate with the activity of DM. An increase was observed in the expression of mRNA of IL-6 in muscle tissues of patients with PM and DM, but not in normal muscles. Okiyama et al. have shown that IL-6 is expressed in macrophages infiltrating muscle tissues, and that the administration of monoclonal anti-IL-6 receptor antibodies prevented the appearance and progression of the inflammatory myopathy.

**Interferon**

In the muscle tissue and peripheral blood of patients with DM and PM, IFN gene expression has been observed and can be associated with disease activity.

Interferon activates natural killer cell cytotoxicity, promotes T lymphocyte activation and survival, and dendritic cell maturation, in addition to enhancing MHC class I expression by muscle fibers. On the other hand, IFN-regulated proteins (IP-10, I-TAC, MCP-1 and MCP-2) are elevated and play a role in recruiting lymphocytes for muscle inflammation sites.

The fact that the muscle fibers of patients with IIM express MHC class I antigens implicates that such fibers might behave as antigen-presenting cells for CD8+ T lymphocytes. Based on that hypothesis, Murata et al. have shown that muscle fibers of patients with PM also express the costimulatory molecule BB-1. On the other hand, CD8+ T lymphocytes around those fibers expressed CD28 and CTLA-4. Behrens et al. have reported that muscle fibers expressed BB-1 after stimulation with either IFN-γ or TNF-α.

The use of biologics is supported by those immunopathological findings, particularly in cases of IIM refractory to corticosteroids and several immunosuppressive drugs.

**Shinjo et al.**

(MEDLINE) database. The following terms were assessed: dermatomyositis, biologics, immunobiologicals, immunopathology, polymyositis, drug therapy, and treatment.
Immunotherapy/Immunobiologics

Anti-TNF therapy

**Infliximab**
Infliximab is a chimeric monoclonal antibody against TNF-α, composed by a sequence of peptides, 75% human and 25% murine.27

Some reports have shown an improvement in the muscle strength of patients with IIM, and a reduction in the serum levels of muscle enzymes after the treatment with biologics of the anti-TNF-α type.25-30 However, results are not homogeneous. Efthimiou et al.39 have published a retrospective study with 2 patients with DM refractory to conventional treatment (methotrexate and azathioprine). One of the patients had previously used etanercept and intravenous human immunoglobulin, with no change in the myopathic findings. Both patients were treated with infliximab at the dose of 3 mg/kg at intervals similar to those recommended for rheumatoid arthritis. After a mean follow-up of 15.2 months, the patients showed no significant reduction in the serum levels of creatine kinase, and only one of them showed a mild improvement in muscle strength within the first three months of treatment. However, the results of an open-label study with infliximab as the first treatment option, published by Hengstamm et al.34 and using a dose of 10 mg/kg of weight associated with methotrexate, at intervals of 0, 2, 6, 22, 38 and 46 weeks, have not been conclusive due to the high relapse rate and difficulty to include cases, leading to an early end of the study. Another open-label pilot study of infliximab in 13 patients with refractory inflammatory myopathies (5 with PM; 4 with DM; and 4 with inclusion body myositis) used methotrexate as the immunosuppressive agent. The infliximab dose used was 5 mg/kg of body weight at weeks 0, 2, 6 and 14. Four patients discontinued the study (3 due to adverse events and 1 due to the presence of ovarian malignancy). Of the 9 patients completing the study, only 3 had at least a 20% improvement in 3 or more International Myositis Assessment and Clinical Studies Group (IMACS) variables (disease activity score).35

**Adalimumab**
Adalimumab is a fully human monoclonal antibody that blocks the TNF-α molecule directly.40

The use of adalimumab for systemic autoimmune diseases, mainly rheumatoid arthritis, can induce the development of inflammatory myopathies (all descriptions were DM).40–46 That is probably the reason why, due to fear of exacerbating the inflammatory myopathy, there is no description of the use of adalimumab as drug therapy for patients with either PM or DM.

**Etanercept**
Etanercept is a soluble recombinant TNFα receptor, composed of a dimeric fusion protein with a constant region of human IgG1 and variable regions of murine antibody.37

Iannone et al.38 have reported 5 patients with DM refractory to corticotherapy and to immunosuppressive agents (combination of methotrexate and azathioprine), who received etanercept subcutaneously (25 mg, 2x/week) for a minimum of 3 months. The patients showed no improvement in the cutaneous findings, worsened their muscle weakness, and increased their serum levels of muscle enzymes.

Spratt et al.37 have reported the case of a patient with PM refractory to conventional drug treatment (methotrexate, azathioprine and/or intravenous human immunoglobulin in association with corticosteroids). Because of disease refractoriness, etanercept (25 mg, 2x/week, subcutaneously) was initiated, and corticotherapy was later suspended due to stability of the clinical and laboratory findings. Efthimiou et al.39 have reported the cases of 8 patients (3 with DM) refractory to methotrexate, azathioprine and intravenous human immunoglobulin, who underwent adjunct therapy with etanercept and/or infliximab; 6 patients responded. Of those 8 patients, 6 received etanercept (25 mg, 2x/week), 1 receives infliximab and 1 received sequential therapy with 2 agents. The problem with that report is the concomitance of therapies, which can be a confounding factor in the improvement reported. Six of the 8 patients studied underwent monthly pulse therapy with methylprednisolone, and all of them received intravenous human immunoglobulin (2 g/kg of body weight) associated with etanercept.

**Rituximab**
Rituximab is a chimeric monoclonal antibody directed against CD20 antigen present on the surface of B cells. Its administration leads to the selective depletion of CD20+ B lymphocytes.

Recently rituximab has been used for refractory DM and PM.47–56 Considering the important role of B and T lymphocytes in mediating IIM activity,57–60 However, the efficacy of rituximab in the treatment of PM7,55,56 contradicts the models proposed for the disease pathogenesis, because the depletion of B lymphocytes in PM leads to a satisfactory clinical and laboratory response. In the case of PM, the predominance of the cytotoxic CD8+ T lymphocytic infiltrate in muscles55,57,60 suggests a more important role of B lymphocytes in the
The pathogenesis of PM than previously recognized, acting as costimulatory or antigen presenting cells.

In 2005, a small open-label study with rituximab (100 mg/m² for 4 weeks) was performed with 6 patients with DM refractory to conventional drug treatment (1 had no previous drug treatment and 1 was refractory to previous use of etanercept). Improvement was observed in muscle strength, muscle enzymes and skin lesions, with a peak improvement in muscle strength after 12 to 36 weeks of treatment. All patients had depletion of B lymphocytes. Four patients experienced a return of symptoms that coincided with the return of B lymphocytes. Other parameters, including rash, alopecia and reduced forced vital capacity, improved. Chung et al. treated 8 patients with DM refractory to multiple immunosuppressive drugs, one of whom after etanercept failure, with 2 infusions of rituximab (1 g each, 2 weeks apart). Three patients had improvement of their muscle strength, but significant change was observed in neither the levels of muscle enzymes nor the severity of skin lesions after 24 weeks of drug infusion.

In 2005, Lambotte et al. reported the case of a patient with PM, whose clinical and laboratory findings improved after receiving rituximab (375 mg/m²/week for 4 weeks). Another study has reported the treatment with rituximab (375 mg/m²/week for 4 weeks) of 4 other patients with PM refractory to corticosteroids and methotrexate/azathioprine. In analysis of 28 weeks of medication, all patients improved their muscle strength, and 2 achieved normal strength. The creatine kinase level normalized and the corticosteroid dose was reduced in all cases.

Tocilizumab
Tocilizumab is a humanized monoclonal anti-IL-6 antibody. The only study in the literature describes 2 male patients diagnosed with PM, both positive for anti-Jo-1 antibody. One patient, refractory to corticosteroid (1 mg/kg/day), azathioprine (100 mg/day) and cyclosporine (100–150 mg/day), received tocilizumab (8 mg/kg, monthly, intravenously). After 1 year using the drug, corticosteroid was suspended, and cyclosporine (100 mg/day) maintained. There was evidence of progressive improvement in the muscle strength and laboratory findings. The other patient was refractory to corticosteroid (1 mg/kg/day), azathioprine, cyclosporine and/or methotrexate. Initially he received tocilizumab monthly (8 mg/kg, intravenous), and after the forth dose, the interval was reduced to 3 weeks. After 12 cycles of tocilizumab, associated with methotrexate, the patient showed stability of the clinical and laboratory findings.

Abatacept
Abatacept is a human recombinant fusion protein, containing the extracellular domain of CTLA-4, which binds to the CD 80/86 receptor of an antigen-presenting cell. That interaction blocks the activation of the CD 28 receptor in T cells.

Literature review shows only one case report of a 51-year-old female patient with PM refractory to corticosteroid and methotrexate/azathioprine, who received abatacept (750 mg intravenously, monthly). Her clinical and laboratory findings improved at the beginning of treatment, with normalization of the creatine kinase, aldolase and lactic dehydrogenase levels 3 months after beginning the applications. The response persists after 3 years of follow-up.

FINAL CONSIDERATIONS
The use of biologics for patients with DM and PM remains an unconquered frontier. The literature review yielded a few articles, comprising small non-controlled studies, mainly case reports and series. The TNF blocking agents have conflicting results. In addition, development of IIM during their use have been reported. So far, the most encouraging evidence originates from the anti-CD20 therapy with satisfactory results reported, but still requiring further investigation. The IL-6 inhibition and costimulation blockade in IIM have been only anecdotally reported, and, so far, no conclusion has been extracted from them.

Thus, biologics might play a relevant role in the management of IIM refractory to conventional therapy. However, evidence justifying that approach might only be produced by use of new prospective studies based on objective parameters of response to treatment. So far, anti-CD20 therapy seems to be the most promising treatment for refractory IIM.
REFERENCES


