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A therapeutic perspective for refractory polymyositis to corticosteroids and immunosuppressant drugs: A case report

Dilceu Silveira Tolentino Junior[1]

1 School of Medicine, Federal University of the Jequitinhonha and Mucuri Valleys, Teófilo Otoni, Minas Gerais, Brazil

Case Report

Abstract

BACKGROUND: Polymyositis (PM) is a chronic, disabling, and progressive inflammatory disease with muscle and systemic involvement. Although it is uncommon, some patients may present drug resistance to initial treatment with corticosteroid and immunosuppressant drugs.

CASE REPORT: In this study, a typical case of poor prognosis of a 40-year-old female with PM who presented resistance to the initial treatment with corticosteroids and immunosuppressants was presented. The first medication tested was prednisone for 30 days and then 5 pulses of methylprednisolone were performed for 5 months, and since there was no effect, a combination of azathioprine and methotrexate was performed for 8 months, which was also unsatisfactory. Then, the scheme was changed to cyclophosphamide, human immunoglobulin (HIG), and cyclosporine, which were also unable to change the clinical course of the disease, which led the prescriber to radically change the drug therapy to the immunobiological rituximab (RTX), the only medication capable of ensuring an excellent therapy response and recovery of muscle strength.

CONCLUSION: This report demonstrates the importance of the necessary persistence for the prescriber to test certain classes and drug combinations in search of the best possible therapeutic response for the specific case, which only occurred after the prescription and proscription of the drugs of first choice and the change to the immunobiological drug, RTX.

KEYWORDS: Polymyositis; Resistance; Corticosteroid; Immunosuppressant; Drugs; Rituximab

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Introduction

Polymyositis (PM) is an inflammatory myopathy that constitutes a heterogeneous group of diseases characterized by proximal muscle weakness and serum elevation of enzymes originating from the skeletal musculature.[1] The etiology of PM remains unknown and its annual incidence is estimated to be less than 10 cases per million individuals. Women are more affected in a ratio of approximately 2:1, with a bimodal peak of onset of the disease between 5-15 years and 45-65 years.[2]

The course of the disease is variable and most patients respond satisfactorily to initial treatment with glucocorticoid and it is possible to identify other evolutionary patterns with an initial remission period followed by one or more episodes of recurrence, monocyclic or refractory to usual treatment.[3] Among the factors of poor prognosis, it is highlighted in the initial diagnosis in the elderly, advanced degree of muscle weakness at the time of diagnosis, respiratory muscle dysfunction, presence of dysphagia, delay at the beginning of treatment after 6 months of onset of symptoms, and pulmonary or cardiac involvement associated with neoplasia.[3,4]

Corresponding Author:
Dilceu Silveira Tolentino Junior; School of Medicine, Federal University of the Jequitinhonha and Mucuri Valleys, Teófilo Otoni, Minas Gerais, Brazil
Email: dilceujunior@bol.com.br

The association of immunosuppressants and corticosteroid from the beginning of treatment should be performed in patients with poor prognostic factors since the number of patients who do not reach remission with isolated corticosteroid therapy is considerable.[5-7] The response to immunosuppressants and corticosteroid will occur approximately 2-3 months after the start of its use, and after this period with the optimized dose, if the patient still presents with clinical and laboratory signs of disease activity, and is not responding as expected, such a therapeutic scheme should be modified[7]. Among the cases treated at this rheumatology clinic, located in the northeast region of Minas Gerais, Brazil, we chose the only case of PM resistant to glucocorticoids (GCs) in follow-up in order to observe the similarities of the case described with the literature.

Case Report

This case report presented a 40-year-old woman diagnosed 11 years ago with PM, confirmed by muscle biopsy, electromyography, and muscle enzymes presented lameness and intense loss of strength of lower limbs and upper limbs. The first prescribed medication was prednisone, with daily dosing of 80 mg for 30 days, and 5 pulses of methylprednisolone for 5 months. Then, the combination of azathioprine and methotrexate was tested for 8 months, which was not successful, modifying to intravenous cyclophosphamide with 1 dose every 4 weeks for about 8 months. However, the disease activity still maintained, which led to the change in the drug regimen for human immunoglobulin (HIG) with 5 daily doses and 1 monthly dose for 9 months that was also unable to evolve to remission of the disease. Thus, the therapeutic regimen was replaced by 150 mg of cyclosporine daily, being 2 tablets of 50 mg in the morning and 1 tablet in the night for 7 months, not gaining good control of the disease again.

Due to the weak therapeutic response to these conventional corticosteroid and immunosuppressant drugs presented in table 1, the prescriber suspended the previously tested therapeutic regimen and based on successful studies described in table 2, decided to experiment with rituximab (RTX), considering a second-line drug that was not widely used for the treatment of inflammatory myositis.

Table 1. First choice drugs and posology for the conventional treatment of polymyositis (PM)

Variables
Prednisone: 5 and 20 mg tablets (maximum 80 mg/day); **Methylprednisolone:** powder for the injectable solution of 500 mg (administered 1000 mg intravenously over 1 hour for 3 consecutive days); **Azathioprine:** 50 mg tablets (increasing 50 mg every two weeks to the total dose of 2-3 mg/kg/day); **Methotrexate:** 2.5 mg tablets or 25 mg/ml injectable solution (the dose may be increased to 25 mg/week); **Cyclosporine**: capsules of 10, 25, 50, 100 mg and oral solution of 100 mg/ml - 50 ml (up to a maximum dose of 6 mg/kg/day); **HIG:** a vial of 0.5 g, 1 g, 2.5 g, 3 g, 5 g, and 6 g (1 g/kg/day for 2 days or 0.4 g/ kg/day for 5 days, with a maximum dose of 70 g, repeated monthly for 3 to 6 months in adults) **Source:** Clinical Protocol and Therapeutic Guidelines (Dermatomyositis and Polymyositis), revised in 2016

HIG: Human immunoglobulin

The medication regimen was changed to an intravenous infusion of 1,000 mg of RTX, with an interval of 14 days between doses, the same regimen used for the treatment of rheumatoid arthritis (RA). Before each administration of RTX, premedication was administered with antipyretic (paracetamol) and antihistamine (diphenhydramine) and methylprednisolone 100 mg to decrease the incidence and severity of reactions to the infusion. The initial speed of the first infusion was 50 mg/hour. Thereafter, the speed was gradually increased by 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour.

The patient did not present serious side effects to the administration of RTX, only nausea, mild headache, and fatigue in the 24 hours after administration, however after the observation period, there was no more record of complaints by the patient.

Table 2. Studies testing the response of patients with polymyositis (PM) to rituximab (RTX) therapy

References	Type of study	Number of patients	RTX dosage	Outcome
Valiyil et al.[8]	Moderate/large series/8	8	1 g I.V. at day 0 and 14	Improvement in muscle strenght and CK levels
Gheita et at.[9]	Case report/1	1	500 mg I.V. at days 0 and 14	Significant improvement in muscle and CK levels
Mok et al.[10]	Open label/4	4	375 mg/m² weekly for 4 weeks	Significant improvement in the mean proximal muscle power scores and reduction in CK levels
Belhassen-Garcia et al.[11]	Case report/1	1	375 mg/m² weekly for 4 weeks	Improvement in muscle strenght and CK levels

CK: Creatine kinase

The patient received an additional course of treatment 16 weeks after the first infusion for adequate control of the effect/response, in addition to ensuring the effectiveness and safety of maintaining the next therapeutic courses. The prognosis did not require dose adjustment during treatment and, after 7 months of maintenance of the therapeutic course, the patient's health status remained satisfactory, with significant improvement in muscle strength and with a creatine kinase (CK) enzyme level of around 159.0 U/L, considered a normal value.

Discussion

Although in the present case study the use of glucocorticoid alone was not able to change the course of the PM favorably, the use of glucocorticoid can induce remission of the disease in approximately 40% to 60% of the patients. However, more than 80% present some degree of clinical and laboratory improvement with the treatment and patients should be informed that corticosteroid therapy may last longer than 12 months.[6,7]

The variability of responses to the use of corticosteroids in the treatment of various inflammatory diseases is a known effect in the clinical setting. Although many patients present satisfactory responses to corticosteroid therapy, a small subpopulation of individuals fails to respond to the therapeutic effects of this class of medications. Based on this, patients can be classified as resistant to corticosteroids (RC).[12] The magnitude of the biological effects of these drugs is determined, among other factors, by the amount of target cell receptors and the receptor affinity to glucocorticoids.[13]

In the evidence of disease activity (resistant disease), there is a need for increased or resumed glucocorticoid dose (relapsing disease), as well as intolerance to methotrexate or azathioprine, and should be considered a therapeutic modification. In this way, it is recommended to change the methotrexate by azathioprine or azathioprine association with methotrexate.[14]

As in the case study, the association of azathioprine with methotrexate did not achieve the desired effect and pulse therapy was performed with methylprednisolone and should always be considered in cases of severe muscle weakness or severe systemic involvement.[11] In the absence of response to the above measures, due to intolerance or relapse, it is recommended to replace the treatment previously used by cyclophosphamide, human immunoglobulin (HIG), or cyclosporine. The glucocorticoid should be maintained until control of disease activity. An option for resistant or intolerant patients to the drugs described is HIG.[14-16]

Because it is an uncommon disease, PM drug therapy is based primarily on reports or series of cases. In general, the use of corticosteroids has been advocated as the drug of the first choice, and as a way to avoid these medications, several immunosuppressants are used as was used in the case described. However, a considerable number of patients do not respond satisfactorily to these traditional treatments. In

these cases, the immunobiological drug is used based on the pathophysiology of PM, especially RTX,[17] the only therapeutic resource that was able to modify the course of the disease in the case studied.

RTX is a chimeric monoclonal antibody directed against the CD20 antigen present on the surface of B cells. Its administration leads to selective depletion of CD20 + B lymphocytes.[17] The experience of RTX therapy in the present case study was positive as it provided excellent disease control after 6 months of use, which can be compared to the study by Valiyil et al.[8] who observed 8 patients using 1 g I.V. of RTX on days 0 and 14, the study by Gheita et al. [9] who observed the case of 1 patient who used the 500 mg I.V. dosage on days 0 and 14, and the open study by Mok et al.[10] with 4 patients and the case study by Belhassen-Garcia et al.[11] with 1 patient, who used 375 mg/m² weekly for 4 weeks. All of these studies showed a satisfactory response, as did the present case study, with significant improvement in muscle strength and reduction in serum CK levels.

Thus, immunobiological therapy with RTX played a crucial role in the control of refractory PM to conventional therapy. However, only with new prospective studies based on objective parameters of response to treatment can evidence be produced to justify such conduct.[13]

Conflict of Interests

Authors have no conflict of interests.

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