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*Brief Report*

## **Long-Term Remission of Severe Refractory Dermatopolymyositis with a Weekly-Scheme of Immunoglobulin Followed by Rituximab Therapy.**

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## **Introduction**

Dermatopolymyositis (DM/PM) is a life-threatening systemic inflammatory disease characterised by substantial muscle weakening, cutaneous lesions, cardiac and lung impairment. Idiopathic inflammatory myopathies comprise a heterogenous group of autoimmune disorders that include polymyositis (PM); dermatomyositis (DM) and other related conditions whose causes and pathogenesis remain unclear. In DM, inflammatory changes occur both in muscle and skin. Although its cause is unknown, autoimmune mechanisms are implicated [1-3]. The first line of treatment for DM/PM consists of corticosteroids alone or in conjunction with other immunosuppressive drugs. Among second-line therapies for patients that present with DM/PM resistant to conventional treatments or with severe drug-induced side effects, intravenous polyvalent immunoglobulin (IVIG) represents an effective and safe alternative. There have been some case reports and open label trials on the beneficial effects of Rituximab (anti-CD20 monoclonal antibodies) in DM/PM [4,5]. We report on a 44 year-old woman affected by DM/PM resistant to conventional therapies who experienced clinical improvement and remission after 2-year treatment with IVIG in a weekly schedule followed by Rituximab therapy.

### **Case report**

A 44-year-old Caucasian woman diagnosed as having DM/PM for 3 years was referred to our Clinical Immunology Unit due to persistence of DM/PM signs and symptoms in spite of treatment with high-dose systemic corticosteroids. She had been treated with oral prednisone up to 1.5 mg/kg body weight/day, monthly intravenous methyl-prednisolone pulses, methotrexate and azathioprine. The latter two were discontinued because of drug intolerance. Specific myositis autoantibodies were negative. Muscle weakness and fatigue worsened despite therapy with oral prednisone and methyl-prednisolone pulses. She was given IVIG (Flebogamma® 10%, Grifols S.A., Barcelona, Spain) at the dose of 2g per kg of body weight during 5 consecutive days per month for the first 6 months. Serum aldolase and LDH levels were elevated prior to IVIG treatment (8 UI/L and 518 UI/L, respectively) and they both declined to normal values 1 month after the first IVIG cycle (Figure 1 and 2). During the first 6 months of IVIG treatment, the initial prednisone dose of 90 mg/day (1.5 mg/kg/day) was progressively tapered to a maintenance dose of 5 mg/day, while achieving clear clinical improvement in muscle strength with no significant side effects. She was then given a maintenance treatment with an IVIG protocol of weekly infusions of 400 mg/kg/week for other 6 months, with persistent control of clinical and biochemical manifestations. After that, she was progressively placed on a maintenance protocol consisting of an IVIG dose of 200 mg/kg every other week, showing remission of DM related symptoms. Unfortunately,

every attempt to further reduce the IVIG dosage or to prolong intervals of administration resulted in an early increase in LDH levels and worsening of symptoms. Even though IVIG therapy resulted in sustained clinical improvement throughout the first two years of treatment, after that period the patient started to present a decline in treatment response and remission of symptoms. We decided to switch her to rituximab (anti-CD20 monoclonal antibodies, Mabthera®, Roche) IV infusions at a dose of 375 mg per m<sup>2</sup> of body surface administered weekly for a total of 4 doses. Rituximab treatment was well tolerated. Approximately 1-week after the fourth dose of rituximab treatment, the patient experienced marked and progressive clinical improvement, particularly in her asthenia and muscle strength. This effect lasted for 6 months, after which maintenance schedule of rituximab at a dosage of 1g IV two weeks apart was given, with an excellent clinical response. Due to hypogammaglobulinemia secondary to rituximab treatment associated with recurrent upper respiratory tract infections, our patient was given IVIG therapy at a low maintenance dose of 200 mg per kg of body weight every 4 weeks. As of the time of this writing, the patients' muscle strength and quality of life have improved dramatically up to the point that she is now able to maintain an acceptable physical activity, including weekly swimming practice.

## **Discussion**

In addition to their original administration as antibody replacement therapy, immunoglobulin preparations have also been used to treat several autoimmune and systemic inflammatory diseases due to its anti-inflammatory and immunomodulatory effects [6,7]. One of the new modalities in the treatment of patients with DM unresponsive to conventional therapies has been the usage of high-dose IVIG at a classical schedule of 2 grams per kg of body weight administered over 5 days. Indeed, a double-blind placebo-controlled study has shown that IVIG is very effective in improving both muscle strength and skin rash [8]. Quantitative histological studies in repeated muscle biopsies have also shown a statistically significant increase in the size of muscle fibers and the number of capillaries with normalization of the capillary diameter, resolution of aberrant immunopathological parameters, and modification of immunoregulatory and structural genes in DM patients treated with IVIG [9].

The IVIG infusions are an alternative therapy as steroid-sparing agents in those patients who have shown to be either refractory or dependent on steroids. In particular, our patient had developed major side effects associated with steroid treatment without adequate clinical improvement. She was also intolerant to methotrexate and azathioprine. After high-dose IVIG, there was a rapid improvement in the patient's condition that correlated well with a reduction in the levels of biochemical markers of muscle inflammation.

There are encouraging results in individual case reports and small series on the use of rituximab for the treatment of severe and refractory DM/PM, similarly as its effects on other immune-based diseases, whose mechanism of action is not completely understood [4,5]. Although rare, adverse effects are an important concern of the treatment with rituximab, such as the potentially severe infusion-related reactions and the occurrence of opportunistic infections, malignancy and activation of latent viral infections [10], among others [11].

Even though we initially suggested that treatment with high-dose IVIG or long-term weekly IVIG maintenance scheme may be useful as a steroid-sparing agent in patients with DM refractory to conventional therapies or intolerant to immunosuppressive drugs, rituximab seems to be a safe and effective alternative option in those patients who fail to sustain remission. Rituximab induces a depletion of B cells, and in selected patients can cause hypogammaglobulinemia, with increased risk of infections. We propose the usage of IVIG therapy as a first step in refractory DM/PM patients, which avoids hospitalisations and improves the patient's quality of life, followed by Rituximab therapy as a second step for non-responding patients. Additional multicenter clinical studies should be necessary to further confirm the efficacy of both alternative therapies for PM and DM, in order to establish better recommendations in the future.

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The authors declare that they have no conflict of interest.





