CASE REPORT

Treatment of refractory juvenile dermatomyositis with tacrolimus

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Abstract We report the clinical course of three patients with refractory juvenile dermatomyositis (JDM) who were treated with tacrolimus. All three children had extensive skin disease and severe muscle weakness and were corticosteroid dependent. All three patients showed impressive improvement of mainly the cutaneous lesions. Furthermore, overall disease activity decreased, all children became more physically active, and corticosteroid treatment could be tapered. However, none of the patients showed recovery of muscle strength, which was most likely due to irreversible muscle damage related to the long-standing myositis and/or high-dose steroid treatment. Patients were followed up for 7 to 9 months after the introduction of tacrolimus. No adverse effects were seen. These cases demonstrate that tacrolimus has beneficial effects in children with refractory JDM, especially in those with severe cutaneous manifestations.

Keywords Juvenile dermatomyositis · Tacrolimus

Introduction

Juvenile dermatomyositis (JDM) is the most common of the paediatric inflammatory myopathies and is characterised by proximal muscle weakness and rash. Corticosteroids are the treatment of choice and have dramatically reduced morbidity and mortality rates in the past decades [1]. Second-line agents used to treat steroid-resistant disease or to induce steroid-sparing effect in children include methotrexate (MTX), intravenous immunoglobulins (IVIG), cyclophosphamide, cyclosporine A, hydrochloroquine, mycophenolate mofetil (MMF), rituximab and TNF-alpha antagonists [1]. Tacrolimus, an inhibitor of T-cell activation and proliferation, is one of the new therapeutic options for JDM. Little is known about its efficacy in this patient group.

Therefore, the goal of this case report is to describe our experiences with tacrolimus in JDM patients. We present three children with refractory JDM who showed positive responses to oral tacrolimus.

Case reports

Case 1

A 6-year-old boy was diagnosed with JDM in December 2002. Treatment was started with prednisolone 2 mg kg⁻¹ day⁻¹. Substantial improvement of the severe muscle weakness was not achieved until after additional treatment with MTX, intravenous IVIG and rituximab in the 3 months following admission. In the following years, relapses occurred despite the medication and were treated with methylprednisolone pulse therapy and IVIG. MTX was switched to MMF, and hydrochloroquine was added. Muscle strength remained stable in this period. Childhood Myositis Assessment Scale (CMAS) score was between 36 and 40 (maximum score 52). In September 2006, recurrence of severe myositis, accompanied by dysphagia and vasculitis of the skin, led to prolonged admission. Increase of the steroid dose and administration of
rituximab did not improve his condition. The patient became dependent on nightly oxygen, most likely due to respiratory muscle weakness. Starting December 2006, monthly doses of cyclophosphamide were given. Nevertheless, a relapse occurred in April 2007, with predominant involvement of the skin. In July/August 2007, the patient had developed gastrointestinal manifestations of the dermatomyositis which responded well to methylprednisolone pulse therapy. There was diffuse erythema of the face and extremities, and the serum muscle enzyme levels were elevated. Therefore, the decision was made to introduce oral tacrolimus (target serum level 10 μg/l, therapeutic range 5–15 μg/l). Three weeks after starting tacrolimus, the patient had become more physically active, the skin lesions started to resolve, and muscle enzyme levels normalized. In the 7 months of follow-up, the patient was able to walk greater distances, the cutaneous manifestations showed impressive improvement with only very mild erythema in the face, and the prednisolone was tapered down to 0.1 mg kg⁻¹ day⁻¹ without any signs of exacerbation. However, muscle weakness persisted (CMAS 36–38) and was attributed to permanent muscle damage caused by the myositis and steroid treatment. No adverse effects of the tacrolimus were observed.

Case 2

A 6-year old girl was diagnosed with JDM in February 2007 after a 10-month history of progressive proximal muscle weakness. During the prolonged admission that followed, the patient was first treated with methylprednisolone pulse therapy, followed by oral prednisolone 2 mg kg⁻¹ day⁻¹ and MTX. Due to further loss of muscle strength, cyclophosphamide and rituximab were administered. Still, she suffered from severe myalgia, had a CMAS score of 4 and was bedridden. She also had extensive skin lesions in the face, trunk and legs, and the muscle enzymes remained elevated. Consequently, tacrolimus was initiated in June 2007 while prednisolone (0.8 mg kg⁻¹ day⁻¹) and MTX (20 mg m⁻² week⁻¹ s.c.) were continued. Improvement started to show 2 to 3 weeks after initiation of tacrolimus treatment. There was no myalgia, and the patient was increasingly mobile, although there was still severe muscle weakness with a CMAS score of 10 and muscle contractures in the lower extremities that severely impaired further ambulation. Skin involvement was significantly reduced, and the serum muscle enzyme levels decreased gradually. In the following 4 weeks, she participated more in daily activities, and the skin lesion continued to improve. No side effects of the tacrolimus were seen in the 9 months of follow-up. Because of the severity of the disease activity, after reaching remission status with tacrolimus, autologous bone marrow transplantation was performed.

Case 3

A 4-year-old girl was diagnosed as having JDM in March 2003. She initially responded to treatment with prednisolone 2 mg kg⁻¹ day⁻¹ and IVIG. However, she relapsed during tapering of the prednisolone. Steroid pulse therapy, MTX and IVIG were needed to control disease activity. In the second half of 2004, increased muscle weakness, vasculitis of the skin and extensive calcifications that first started in the lower extremities and later involved the upper extremities were observed. A new course of IVIG did not improve the skin involvement. Subsequently, rituximab was given to stabilise disease activity and taper down the prednisolone. However, tapering of the steroids again led to increased myositis and skin activity. As the patient was becoming increasingly impaired in daily activities despite additional treatment with MMF (1 g/day) and hydrochloroquine, tacrolimus was introduced in July 2007. At that time, muscle enzyme levels were within normal range, and CMAS score was 28. Two weeks later, improvement of the skin disease was observed. In the following 8 months, most of the cutaneous lesions disappeared, the patient became more energetic and was even able to run again. The prednisolone dose was reduced to 0.15 mg kg⁻¹ day⁻¹. No side effects of the tacrolimus were observed.

Discussion

Tacrolimus is a calcineurin inhibitor that suppresses the IL-2-dependent T-cell activation [2]. It is widely used in transplant medicine and has been shown to be effective in several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease [3–5]. Beneficial effects of tacrolimus have also been demonstrated in adult polymyositis and dermatomyositis [6–10]. Little is known about the efficacy of systemic tacrolimus in juvenile dermatomyositis. There have been three case reports on this topic [11–13]. Yamada et al. reported a 13-year-old girl with steroid-dependant JDM who was previously treated with MTX, azathioprine, IVIG and cyclosporine A [11] and showed significant improvement only after introduction of tacrolimus. Three other children were described by Modesto et al. [12]. After 1 year of tacrolimus treatment, muscle strength normalised in all three patients, skin abnormalities resolved completely in two children and improved substantially in the third and steroid treatment could be discontinued in two children, while the dose was tapered in the third. Finally, in a report of six children, who were given tacrolimus for 1 year, Martin Nalda et al. showed significant improvement of both muscle strength and skin disease [13].
The three case descriptions presented in the current report also suggest beneficial effects of tacrolimus treatment. All three patients had extensive vasculitis of the skin and severe muscle weakness. The skin lesions improved greatly in all patients but did not resolve completely during the follow-up period of 7 to 9 months. The myositis also seemed to respond to the tacrolimus, as muscle enzyme levels normalised in patients 1 and 2, and the myalgia disappeared in patient 2. However, we did not see any improvement of muscle strength. This could be explained by the prolonged disease course and/or high-dose corticosteroid treatment that might have caused irreversible muscle damage or the relatively short follow-up period after controlling the disease with tacrolimus, which may not have allowed the muscles to sufficiently restore their strength. It should be noted that, despite the persisting muscle weakness, all patients indicated feeling more energetic and stronger. It should be noted that, despite the persisting muscle weakness, all patients indicated feeling more energetic and stronger. It should be noted that, despite the persisting muscle weakness, all patients indicated feeling more energetic and stronger. However, we did not see any improvement of muscle strength. This could be explained by the prolonged disease course and/or high-dose corticosteroid treatment that might have caused irreversible muscle damage or the relatively short follow-up period after controlling the disease with tacrolimus, which may not have allowed the muscles to sufficiently restore their strength. It should be noted that, despite the persisting muscle weakness, all patients indicated feeling more energetic and stronger. However, we did not see any improvement of muscle strength.

The most common side effects of tacrolimus are concentration-dependant and include gastrointestinal symptoms, hypertension, nephrotoxicity, neurotoxicity, disturbances in glucose metabolism, hyperkalaemia, tremor, headache and sleeping disorders [2]. No adverse effects were observed in our patients. This is in line with findings from previous case reports that showed tacrolimus inhibits steroid exporters and increases the hormone-binding function of the glucocorticosteroid receptor [14].

In conclusion, this case report indicates that tacrolimus can substantially improve the cutaneous manifestations of JDM. When administered in an early phase, muscle weakness may improve as well. Therefore, tacrolimus should be considered in JDM cases that are refractory to other immunosuppressive medication.

Disclosures None.

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