Safety and Efficacy of Long-term Use of Infliximab in Severe Juvenile Dermatomyositis – 12 Years of Follow-up

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ABSTRACT Juvenile dermatomyositis with emphasized vasculopathy is rare, but the most severe form of the disease, with a poor prognosis with relapsing and chronic course or, in some cases, lethal outcome. We present a case of a 19-year-old Caucasian female, who developed severe acute juvenile dermatomyositis with emphasized multisystem vasculopathy, including retinal vasculopathy and maculopathy (cotton-wool spots, retinal hemorrhages, macular edema) at the age of 8. Due to no response to standard treatment protocols and rapid worsening of clinical symptoms and laboratory findings, a TNF inhibitor (infliximab) was introduced after the third week of treatment resulting in complete normalisation of muscle enzyme levels and complete resolution of eye changes within the next 2 weeks with a gradual general recovery. To the best of our knowledge, this is the first long-term follow-up of an early TNF inhibitor introduction in a patient with acute, severe form of juvenile dermatomyositis and retinal vasculopathy. After 12 years of infliximab therapy, the outcome was excellent, with no side effects throughout the whole treatment.

KEY WORDS: juvenile dermatomyositis, TNF inhibitor, infliximab, retinal vasculopathy, treatment efficacy

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare childhood autoimmune disease affecting the skin and muscles, often leading to severe multisystem complications. Traditional treatments such as glucocorticoids and methotrexate may prove insufficient in refractory cases (1). Tumor necrosis factor-alpha (TNF-α) inhibitors, known for their effectiveness in treating inflammatory diseases, are considered for refractory inflammatory myopathies, including JDM (2). However, what is the most effective treatment for refractory JDM is still unclear (3).

Among refractory cases of dermatomyositis (DM), rare occurrence of ocular retinal manifestations has been associated with more aggressive forms of DM,

posing further challenges in determining appropriate treatment strategies (4).

We present a case of a 19-year-old patient diagnosed with JDM at the age of 8, characterized by prominent vasculopathy, skin alterations, multisystem involvement, and bilateral retinal vasculopathy, including cotton-wool spots (CWS). Despite prior treatment with standard multidrug therapy proving ineffective, the early introduction of the TNF inhibitor infliximab resulted in an excellent outcome. The patient has been using infliximab for 12 years without experiencing any side-effects.

CASE REPORT

An eight-year-old girl was admitted to our Department in 2011 due to proximal muscle weakness and skin changes, including Gottron's papules and Gottron's signs (Figure 1, a), as well as bilaterally decreased vision. The skin changes predominantly affected sun-exposed areas, namely the face and arms. Initial symptoms included illegible handwriting presenting 6 months earlier, followed by lower leg pain. JDM was diagnosed according to Bohan and Peter criteria (5). MR of the thigh revealed diffuse inflammatory muscle changes. At admission, the childhood myositis assessment scale (CMAS) was 10 out of 52. Opthalmic examination revealed bilateral retinal hemorrhages, CWS, and macular edema (Figure 2, a). Laboratory findings were as presented in Figure 3.

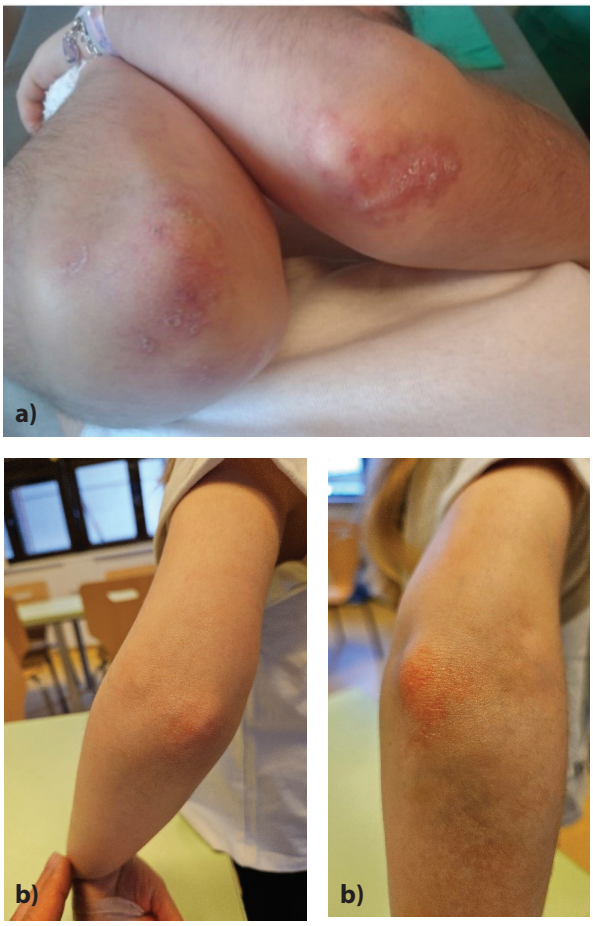

Figure 1. a) Gottron's papules presenting at the beginning of the disease course; b) resolution of Gottron's papules after treatment.

Initial treatment consisted of methylprednisolone (pulse doses – 30 mg/kg/day for 3 days, followed by 2 mg/kg/day) and methotrexate (MTX) (15 mg/m^2/weekly). Rapid progression occurred in the second week, with diffuse vasculitic rash, extreme progressive muscle weakness, nasal speech, extreme swallowing difficulties, progressive dyspnea, and altered consciousness. Despite intensive therapy, including IVIG, plasmapheresis, antibiotics (for pneumonia), and supportive care, the symptoms worsened, and creatine kinase (CK) (Figure 2) levels continued to rise, with a lethal outcome appearing imminent.

On the 24th day of treatment (CMAS 0/52), the TNF inhibitor infliximab was introduced (at a dose of 6 mg/kg, and at weeks 2, 6, and every 8 weeks thereafter). This led to the normalization of CNS functions, regression of retinal vasculopathy, and rapid improvement in laboratory findings (Figure 3) within the next two weeks. Swallowing function recovered completely, and slow muscle strength improved within the next two months. Skin changes (diffuse vasculitic rash) gradually improved over the course of 18 months, and calcinosis never developed (Figure 1, b). After 15 months, the patient achieved complete laboratory remission (Figure 3), with the disappearance of ocular symptoms (Figure 2, b). After 25 months, the patient achieved a full score on CMAS (52/52). Infliximab was discontinued after 24 months of clinical remission, with MTX treatment being continued. The patient remained in complete remission for the next 26 months, until experiencing a clinical (muscle weakness, CMAS 37/52) and laboratory (high CK and lactate dehydrogenase) relapse. Reintroduction of infliximab led to another complete remission. 12 years after, the patient remains in remission under continuing infliximab therapy and without experiencing any side-effects despite the long-term treatment.

DISCUSSION

The use of tumor necrosis factor (TNF) inhibitors in refractory dermatomyositis (DM) has demonstrated benefits in both adult and juvenile patients (6). JDM, with its very low incidence, poses challenges in treatment due to limited clinical trials and reliance on the rheumatologist's experience (2,6). Early and aggressive management with high-dose

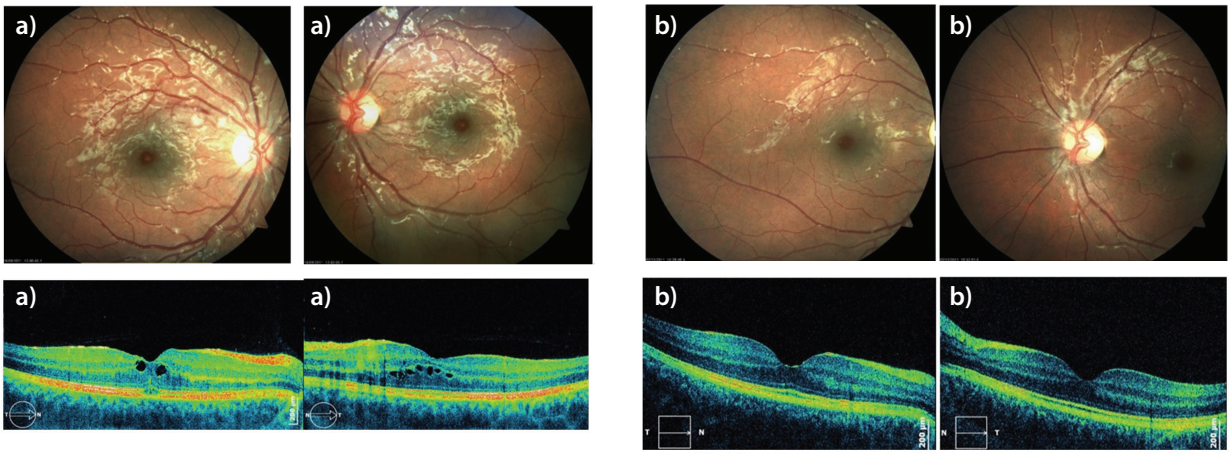

Figure 2. a) Retinal cotton-wool spots, hemorrhages, and macular edema with cystoid changes before the infliximab introduction seen in fundus color photography and optical coherence tomography; b) Regression of retinal hemorrhages, cotton-wool spots, and macular edema (15 months after infliximab introduction) seen in fundus color photography and optical coherence tomography.

glucocorticoids, along with the addition of disease-modifying drugs, is still considered key to achieving complete and sustained remission (2). However, treating refractory patients presents the greatest challenge. Less aggressive initial treatment was identified as a dominant risk factor for a prolonged course of JDM and the development of complications such as calcinosis and lipodystrophy. While a wide range of medications has been tried tried in these difficult cases, there is no clear consensus on which medication should be used (2).

In view of this, we describe an excellent outcome following the early introduction of infliximab in the treatment of an 8 years old female patient with JDM with emphasized vasculopathy, refractory to all previous standard multiple drug therapy, with a long follow-up of 12 years.

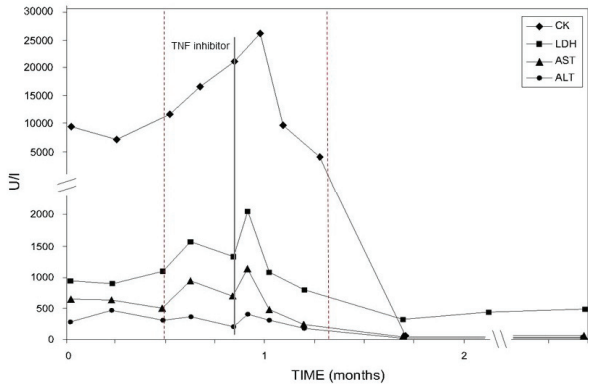

Figure 3. Laboratory findings: levels of creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanin aminotransferase (ALT) during the first two months of treatment. The vertical line ("TNF inhibitor") marks the time of infliximab introduction (24th day of treatment), while red dotted lines mark the appearance and resolution of retinal cotton-wool spots.

In 30-50% of patients, skin disease precedes the occurrence of myositis by 3 to 6 months, while only 10% of patients, including ours, present with muscle symptoms before developing cutaneous manifestations (7). 15 months after starting the infliximab treatment, our patient achieved complete laboratory remission and disappearance of CWS, retinal hemorrhages, and macular oedema. Skin changes regressed after 18 months, while the patient achieved a full score on CMAS (52/52) after 25 months, which is excellent considering that only 30-50% of patients manage to achieve remission within 2-3 years of JDM onset with early treatment (8). Furthermore, early aggressive treatment, such as infliximab treatment, has been shown to reduce the incidence of calcinosis and effectively address skin manifestations (8,9). Despite the patient's severe and uncontrollable disease onset, early infliximab treatment likely prevented further cutaneous complications, with no development of calcinosis.

Our results are consistent with reports of favorable outcomes with the use of TNF inhibitors in patients with JDM resistant to standard multidrug therapy (9,10), although there have been three reports with unsatisfactory results in treating refractory IM (including DM) with infliximab (9). A singular large study retrospectively analysed a cohort of 60 patients with JDM treated with TNF inhibitors (infliximab or adalimumab), finding a general improvement in disease activity. However, 23% of patients treated with infliximab switched treatment due to inefficacy or adverse events. It is noteworthy that the inclusion criteria for this study required TNF inhibitor therapy lasting for

a minimum of merely three months, and the patient clinical data were collected over only 12 months (6).

Ocular complications posed an additional difficulty in treating our patient. With a low prevalence of ocular complications (0.07%) in dermatomyositis, there have been limited reports on the treatment of these patients (11). Since cotton wool spots, which are a sign of serious vascular damage, have been reported to resolve over a period of several months, their resolution after only two weeks of infliximab is remarkable, also suggesting its efficacy in addressing refractory cases linked to CWS (12,13).

CONCLUSION

This rare long-term follow-up of a patient with JDM with CWS emphasizes the success of infliximab treatment over a period of 12 years without any side-effects. This suggests that early consideration of infliximab in the treatment of severe, progressive JDM cases with ocular involvement may be warranted, suggesting its consideration in early treatment for severe, progressive JDM cases with ocular involvement.

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