Effectiveness of infliximab in the treatment of refractory juvenile dermatomyositis with calcinosis

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Objectives. Some juvenile dermatomyositis (JDM) patients have a disease course which is refractory to multiple drug treatments. Prolonged disease activity is associated with increased mortality and morbidity. TNF-α has been identified in high levels in JDM patients who have a long disease course and calcinosis. We assessed the response of five refractory JDM patients to the anti-TNF-α monoclonal antibody, infliximab.

Methods. For all five patients intravenous infliximab was initially given at a dose of 3 mg/kg. Further doses were then given at weeks 2, 6 and every 8 weeks thereafter. The dose and frequency were tailored in accordance with clinical response. Clinical and laboratory data were collected prospectively.

Results. We report results between 8 and 30 months after starting infliximab. Improvements were seen in all five patients as shown by positive changes in physician visual analogue scale (VAS), Childhood Myositis Assessment Score (CMAS), Childhood Health Assessment Questionnaire (CHAQ), joint range of movement and, in some, regression of calcinosis and skin signs. There were no major side effects observed with addition of infliximab to the therapeutic regime.

Conclusions. Major clinical benefit was demonstrated after the initiation of infliximab in all five cases of refractory JDM.

KEY WORDS: Juvenile dermatomyositis, Calcinosis, Refractory, Anti-tumour necrosis factor treatment, Infliximab.

Introduction

Juvenile dermatomyositis (JDM) is a rare chronic inflammatory disease of children characterized by inflammation of muscles, skin and other organs. Mortality is now rare but moderate or severe disability over the medium to long term is still experienced in 8% of patients [1]. Some patients have a disease, which is refractory to existing treatments, which include corticosteroids (CS), methotrexate (MTX), cyclosporin (CIS), intravenous immunoglobulins (IVIG), azathioprine and cyclophosphamide (CYP). Calcinosis can be a debilitating complication of JDM, resulting in joint contractions and calcinotic infections. Unlike adult DM, increasing calcinosis in JDM is considered to be a sign of active disease. There is some evidence that prolonged active disease is related to this complication and that its incidence can be reduced by earlier disease control [2]. Once established, calcinosis is difficult to treat, with only isolated case reports detailing any treatment success [3, 4].

Blockade of TNF-α-mediated action has been successful in treating various chronic inflammatory disorders including juvenile arthritis [5], rheumatoid arthritis [6] and spondylarthropathy [7]. Efficacy of anti-TNF-α therapy has also been described in the treatment of adults with myositis [8] and has been reported in JDM with etanercept [9]. TNF-α has been identified in high levels in JDM patients who have a long disease course and calcinosis [10]. TNF-α has also been identified in fluid collections or ‘milk of calcinosis’ in JDM [4]. Till now there are no indications as to which of the anti-TNF-α therapies is best in JDM: Our unit chose infliximab as it ensured compliance and allowed close monitoring of clinical changes and side effects. Our goal was to control signs and symptoms due to inflammation and to wean corticosteroid therapy. Here we report our experience in treating refractory JDM by administering the monoclonal antibody to TNF-α, infliximab.

Patients and methods

All five patients fulfilled the Bohan and Peter classification for definite or probable JDM [11]. Clinical and laboratory data were collected prospectively in one centre, where all treatments were administered. All five patients presented with typical JDM rash, proximal muscle weakness and grossly raised creatine kinase (CK). Four patients had inflammatory myopathy confirmed on biopsy. We defined severe refractory JDM as evidence of active disease, with progressive calcinosis, despite multiple treatment modalities including physiotherapy and pharmacological therapies. Therapies used included at least two DMARDS (one of which was MTX), and the use of intravenous methylprednisolone, for remission induction.

Clinical condition was assessed using the physician visual analogue scale (VAS). Muscle involvement was measured using the Childhood Myositis Assessment Score (CMAS), a score that has been validated for JDM that measures muscle strength, stamina and function [12]. The Childhood Health Assessment Questionnaire (CHAQ) was used as an assessment of disability [13]. Calcinosis was assessed clinically and with sequential X-rays. It has been our experience that plain X-ray films will pick up calcinosis that has not been palpated clinically. The combination of clinical examination and X-ray gave the best guide as to the current extent of calcinosis.

The laboratory measures used to document muscle disease activity were CK and lactate dehydrogenase (LDH). ESR was used as a measure of systemic inflammation. Any adverse effects that occurred during the period of treatment were also noted.

The intravenous infliximab course was given at a dose of 3 mg/kg at the start of treatment and then at weeks 2, 6 and then every 8 weeks thereafter. It is now our practice to start at 6 mg/kg and increase the frequency to a maximum of 4-weekly dependent on clinical response.

Results

The clinical characteristics of the children, prior to starting infliximab, are shown in Table 1. Clinical data on the five cases,
from the time of starting infliximab onwards, are presented in Table 2. No major side effects were seen in any of the patients. All patients remain on infliximab therapy.

### Case 1

An 8-yr-old girl had been suffering from refractory JDM with continuous active muscle and skin disease. Tender calcinosis and multiple contractures in all limbs were causing severe joint restriction and major disability to the extent that the child was wheelchair bound. Her disease had not responded to DMARDs including MTX, IVIG, CIS and CYP (Table 1). Oral CYP was discontinued due to ongoing disease, despite 2 yrs of therapy, and infliximab was introduced. Osteoporosis was present and pamidronate (PMD) was also introduced. After the first year of anti-TNF-α therapy there was a marked increase in upper body strength as shown by an increase in CMAS from 3/53 to 17/53. The joint range of movement in all joints was greatly improved. Muscle weakness, active skin disease, progressive joint contractures and painful calcinosis were resistant to multiple treatments (Table 1) including PMD, in this 8-yr-old boy. After the first year of infliximab treatment, there was a marked improvement in muscle function (CMAS), disability (CHAQ) and in joint range of movement. The calcinosis was softer, less painful and had regressed dramatically. This prompted a change in the interval of infusions to 12-weekly. Nine months later the patient reported that new calcinotic nodules had appeared. The frequency was increased to 6-weekly and from this point no new nodules were found. However, the existing nodules did become larger of skin disease, prompted a change to 6-weekly treatments, which resolved the lethargy. Skin activity persists despite a dose increase to 6 mg/kg, but, after 2 yrs of infliximab treatment, the improvement in muscle strength, range of movement, lethargy and growth are maintained. The child is now able to stand with support. One episode of an infected calcinotic abscess occurred with good response to anti-staphylococcal therapy.

### Case 2

Muscle weakness, active skin disease, progressive joint contractions and painful calcinosis were resistant to multiple treatments (Table 1) including PMD, in this 8-yr-old boy. After the first year of infliximab treatment, there was a marked improvement in muscle function (CMAS), disability (CHAQ) and in joint range of movement. The calcinosis was softer, less painful and had regressed dramatically. This prompted a change in the interval of infusions to 12-weekly. Nine months later the patient reported that new calcinotic nodules had appeared. The frequency was increased to 6-weekly and from this point no new nodules were found. However, the existing nodules did become larger of skin disease, prompted a change to 6-weekly treatments, which resolved the lethargy. Skin activity persists despite a dose increase to 6 mg/kg, but, after 2 yrs of infliximab treatment, the improvement in muscle strength, range of movement, lethargy and growth are maintained. The child is now able to stand with support. One episode of an infected calcinotic abscess occurred with good response to anti-staphylococcal therapy.
and infected. Two and half years after initiation of infliximab the patient had been weaned off prednisolone and although mild skin disease and calcinosis persists, the overall condition has much improved.

**Case 3**
A 7.5-yr-old boy had refractory JDM with muscle weakness, profound lethargy, skin disease, joint pain and restriction, and painful calcinosis. Previous therapy included MTX, CIs and intravenous CYP. Infliximab therapy was introduced. PMD was also started at this stage due to osteoporosis. His mother reported that his lethargy and weakness, though much improved, were deteriorating in the 2 weeks before his 8-weekly doses of infliximab. This, coupled with a flare of skin disease and arthritis, prompted a change of the infliximab regime to 6-weekly, which led to improved control of these symptoms. His lethargy was not completely resolved until his dose was increased to 6 mg/kg. Eighteen months after starting infliximab he had been weaned off steroids and his calcinosis had decreased on examination and on X-ray. The significant improvement in muscle strength and CMAS (from 33 to 50 during infliximab therapy) was maintained and his CHAQ score (0.875) now indicates only mild disability. No more joint pain or restriction was evident and only livedo reticularis remained of his skin disease.

**Case 4**
A 6.5-yr-old girl had severe facial erythema, moderate muscle weakness, lethargy, hip joint restriction and progressive non-tender soft calcinosis, despite treatment with MTX, CYP and hydroxychloroquine (HCQ). After 6 months of infliximab therapy her muscle, joint and skin disease were improved. She experienced headaches with the first three infusions. The calcinosis was mildly worse and at this point PMD was introduced. At 1 yr her clinical improvement was maintained though some small new calcinotic nodules were evident. Her mother noted a large improvement in energy levels since the initiation of the therapy.

**Case 5**
A previously very active 6-yr-old girl was experiencing muscle weakness, severe lethargy, arthralgia and non-tender soft calcinosis refractory to treatment, including PMD, azathioprine and MTX (Table 1). Infliximab therapy was initiated. After 8 months an improvement was noted in her muscle function, with CMAS rising from 31 to 40, and resolution of joint pain. The original nodules had become softer and smaller and although new small deposits appeared these also subsequently decreased in size. Parental observations reported a dramatic improvement in her energy levels and she had returned to full participation in recreational and sporting activities.

**Discussion**
The introduction of infliximab therapy produced a sustained major clinical improvement in all five cases of severe refractory JDM. The features of JDM disease that were most improved by the addition of anti-TNF-α therapy included muscle weakness, joint contractures and calcinosis. Skin disease was less well controlled. Calcinosis was still present in these cases, but notably it was softer, painless and, in four cases, was less extensive. Literature describes a decreased incidence of calcinosis in JDM when treated earlier and more aggressively [2]. We suggest that the improved disease control on infliximab treatment was important in slowing the progression of calcinosis. All parents felt that infliximab therapy had improved the clinical condition of their children, but cases 1 and 3 reported increasing lethargy and weakness prior to the next infliximab infusion. Shortening the length of time between infusions improved these symptoms in both cases. A similar waning in clinical improvement between infliximab doses has been reported in ankylosing spondylitis [7]. In these patients, a decrease in the interval was also effective in improving disease control. Increasing the dose produced a clear clinical improvement in Case 3.

Corticosteroids were weaned in all five cases, and stopped in three. This, coupled with improved disease control may help in the prevention of further osteoporosis. All cases described remain on infliximab therapy and at least one other DMARD. The effects of DMARDs in these patients cannot be discounted. Remission induction has been described with infliximab use in adult dermatomyositis with a subsequent relapse 3–4 months after completion. After completion of further infliximab treatment these patients were maintained on MTX and low dose prednisolone [8].

PMD, a bisphosphonate, was used for treatment of osteoporosis and also because of possible efficacy upon calcinosis, as described in a single case report, in JDM, using another bisphosphonate, alendronate [15]. PMD has been shown to decrease the levels of macrophage TNF-α release [15], and may have worked synergistically with infliximab. However, it is important to note that PMD was part of the therapy in cases 2 and 5, before infliximab use, and in these a progression of disease and calcinosis was evident. Also in Case 4, PMD was introduced after gains had been made in muscle strength, skin disease and arthralgia. We have no evidence in this report to suggest that PMD, without infliximab, can improve calcinosis or JDM control.

Before and during infliximab therapy all five cases were having physiotherapy. The increase in muscle strength after infliximab initiation may be explained by work showing that higher levels of TNF-α restrict muscle contractility [16]. Similar work has shown that chronically raised TNF-α levels can increase muscle breakdown [17]. Inhibition of TNF-α may improve the response to muscle building exercises.

Infliximab has been associated in adults with adverse events including infections, demyelination and lymphoma [18], and in one RA case, an initiation of inflammatory myositis [19]. In our five cases no serious side effects were seen. Two patients suffered infections at calcinotic sites. This had been a problem before infliximab treatment and is well described in JDM [20]. One patient experienced infusion-related headaches, previously described in infliximab treatment [6].

High levels of TNF-α have been reported in JDM patients with a long disease course suggesting that it may play a significant role in refractory disease [10]. Our use of infliximab was associated with clinical improvement in five cases that had not responded to multiple treatments. Further clinical studies are required to assess the efficacy of infliximab in JDM, its efficacy with other DMARDs, and to ascertain the optimum timing for treatment initiation and cessation. This will be difficult in refractory JDM owing to small numbers, and multi-centre studies with complex treatment arms will be required.

**Rheumatology key messages**
- All five cases of refractory JDM improved with infliximab therapy, with no major side effects.
- JDM features most improved were muscle weakness, joint contractures and calcinosis.

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References


9 Amarillo CKS. Etanercept is effective in the treatment of polymyositis/dermatomyositis which is refractory to conventional therapy including steroids and other disease modifying agents. Arthritis Rheum 2000;43:S193.


