

Concise report

Infliximab may be effective in the treatment of steroid-resistant eosinophilic fasciitis: report of three cases

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Abstract

Objective. EF is a rare fibrosing disorder that may involve skin and internal organs. Current therapies include moderate- to high-dose glucocorticoids with or without use of immunosuppressives.

Methods. We report three cases of steroid-resistant EF in clinical practice who were treated with 3 mg/kg every 8 weeks infliximab therapy.

Results. All patients noticed an improvement in their symptoms, joint contractures and skin thickening within 8 weeks of starting infliximab therapy, ultimately leading to a drug-free remission (range 1–3 years).

Conclusion. Based on this and other reported cases, infliximab may be beneficial in patients with steroid-resistant EF.

Key words: Infliximab, Eosinophilic fasciitis, Case report, Case series, Anti-tumour necrosis factor antagonists.

Introduction

EF is a scleroderma-like syndrome described in 1974 by Shulman with diffuse fasciitis, eosinophilia and symmetrical woody induration of the skin [1]. The usual stages of the disease progress from oedema of extremities to *peau d'orange* with hyperpigmentation to woody induration with skin tightness. In the majority of patients, the onset of symptoms seems to follow unaccustomed severe exercise [2], use of statins, trauma and insect bites [3–6].

Symptoms of EF include progressive thickening and often redness, warmth and hardness of the skin. Sclerodactyly, nail-fold capillary changes, internal organ involvement and RP are rare and help differentiate EF from SSc. EF may be associated with inflammatory arthritis, and pulmonary, haematological and neoplastic disorders [7–9]. Laboratory findings are variable and may include hypergammaglobulinaemia, peripheral blood eosinophilia and elevated acute-phase reactants. Diagnosis is established by skin, fascia and muscle biopsy.

The majority of the patients with EF respond to moderate- to high-dose corticosteroids [10]. Other agents that have shown some success in patients with either steroid resistance or intolerance include HCQ, AZA, MTX, cyclophosphamide, CSA and anti-thymocyte globulin [10–12]. Histamine receptor antagonists, such as cetirizine and cimetidine [13] have also been used with variable results. We herein report three patients with steroid-resistant EF who responded to infliximab, a TNF chimeric mAb.

Case reports

Patient 1 was a 46-year-old female athlete first seen in July 2002 with a 9-month history of a flu-like illness, fatigue, reduced running capacity (down from 25 miles/week to 7 miles/week) and weight gain (35 pounds over 3 weeks). She also noticed tightening of the skin of her legs and arms, dysphagia to solid food and an intermittent pruritic heat-sensitive rash on her stomach and abdomen. She denied RP. On physical examination, there was firmness of the underlying fascia beneath the skin with mild skin thickening [1 on a 0–3 scale based on modified Rodnan skin score (MRSS)] with a total score of 5 [14]. Although MRSS is not a validated outcome measurement in EF, we relied on this to measure treatment progress due to lack of any other validated clinical outcome measurements. She also had marked soft tissue tenderness.

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In addition, the patient had 1 to 2+ indurations in the subcutaneous tissues of the upper arm, which had a cobblestone appearance typical of fasciitis and with elbow and shoulder joint contractures. Hand examination was normal. No concomitant inflammatory arthritis was noted. Her laboratory data in January 2002 showed a haemoglobin of 13.5 g/dl, platelet count of 330/ μ l, white blood count of 6.7/ μ l with 26% eosinophils. Her ANA and RF were negative. Skin/fascia/muscle biopsy on the later aspect of her left lower leg showed lymphoplasmacytic infiltrate without eosinophils in the deep fascia, with mild muscle fibre atrophy and necrosis in the fascial layer suggestive of EF. She was started on daily prednisone 60 mg and MTX up to 20 mg/week without noticeable improvement over a period of 1 year. Prednisone was subsequently tapered to 40 mg in January 2003 as there was no beneficial effect of prednisone. In May 2003, she was started on infliximab with background prednisone (Table 1) and noted an improvement in her symptoms and skin thickening within 3 months and her MRSS scores improved from 5 to 0. She also noticed marked improvement in her joint contractures and underlying skin induration. She developed a sore throat 1 week after the first infusion but no other adverse or serious adverse events were noted. Infliximab and prednisone were continued for 2 years and then prednisone was stopped in 2005 and infliximab was stopped in June 2006. During her last follow-up in 2008, she reported no disease flares with examination showing normal skin texture, minimal induration, better exercise tolerance and good joint motion.

Patient 2 was a 61-year-old woman who noticed increasing skin thickening of her forearms, arms, chest, abdomen, thighs and lower legs in 1998. This progressed to her whole body except her fingers. In addition, she noticed skin nodules under her skin and painful joint contractures, loss of joint motion and tenderness of her joints. She had marked limitation of activity but denied RP. No inflammatory arthritis was noticed. Skin, fascia and muscle biopsies from her thighs performed in October 1998 were consistent with EF showing thickened collagen in the fascia with perivascular inflammation with lymphocytes, plasma cell, histiocytes and eosinophils. Her laboratory data were notable for a haemoglobin of 15.3 g/dl, platelet count of 243/ μ l, WBC 9.15/ μ l with no peripheral eosinophilia and no monoclonal gammopathy. She was started on high-dose prednisone 60 mg/day for 6 months, 40 mg for 6 months and then tapered off in December 2000 that led to softening of her skin with improvement in her MRSS from 29 to 17 and increased the range of motion in her wrists and elbow joints. However, the skin disease worsened (MRSS 17 to 30 points) after lowering the prednisone dose to <40 mg/day. Tapering was attempted because the patient developed cushingoid features and osteoporosis. Prednisone was restarted at 60 mg every other week and MTX (15 mg/week) was added in July 2002; the dose was increased to 20 mg/week with no clinical response. In March 2003, infliximab (3 mg/kg q 8 weeks) was initiated

TABLE 1 Clinical characteristics of three patients

Patient	Age/sex	Date of first symptom	Tissue diagnosis of EF	MRSS before infliximab	Therapies before infliximab	Infliximab dose/ frequency	MRSS after infliximab	Infliximab duration
1	46/F	2001	May 2002	5	Prednisone 60 mg daily (January 2002 to January 2003) and tapered slowly over the next 2 years, MTX 20 mg/week (May 2002 to August 2003), MTX 10 mg/week from May 2003 to June 2006 then 1.5 mg/month till February 2008	May 2003 infliximab 3 mg/kg every 8 weeks, increased to 5 mg/kg q 8 weeks and stopped in June 2006	0	3 years
2	61/F	1998	October 1998	29	Prednisone 60 mg/day for 6 months, 40 mg for 6 months and then tapered off in December 2000. Restarted due to flare March 2001 at 60 mg every other day and MTX added up to 20 mg/week in July 2002. Prednisone tapered off over the next 3 years (stopped in November 2004) and MTX stopped in December 2003	March 2003 infliximab 3 mg/kg q 8 weeks was started	0	3 years
3	61/F	2004	February 2006	9	Prednisone 40 mg started in February 2006 and tapered off in October 2006, stopped in January 2007	March 2007 infliximab 3 mg/kg q 8 weeks was started and infliximab was stopped in October 2007	0	7 months

and the patient noticed a gradual improvement in her skin thickening along with an increase in her joint range of motion and overall physical function (Fig. 1). In May 2003, infliximab was temporarily discontinued for 5 months due to insurance-related reasons and the patient subsequently noticed a flare with increasing skin thickening. Shortly thereafter, infliximab was restarted and the patient experienced gradual and complete clinical remission with return to full-time work (Fig. 1). Prednisone was tapered off over the next 3 years (stopped in November 2004) and MTX was stopped in December 2003.

Patient 3 was a 61-year-old woman who first presented in December 2005. Her symptoms started in September 2004 when she noticed a right forearm nodule and subsequently developed skin thickening and contractures of her feet, ankles, wrists and elbow joints bilaterally. On examination, she also had restricted range of motion of her shoulder, wrist and knee joints bilaterally and a poor handgrip. No inflammatory arthritis was observed. She had 3+ induration of the skin on her ankles and feet bilaterally with no sclerodactyly. She complained of tenderness and bodily pain, but denied RP. Her laboratory data showed haemoglobin of 12.6 g/dl, platelet count of 262/ μ l, WBC count of 7.9/ μ l with 18% eosinophilia and CRP of 1.0 mg/dl. No monoclonal gammopathy was identified. Skin, fascia and muscle biopsy in February 2006 on her left lower leg showed epimyoeal inflammation, fibrosing dermal process with linear infiltrate of lymphocytes, which was consistent with EF. She was started on oral prednisone at 40 mg/day in 2006 and slowly tapered off over the next 8 months due to lack of response and was stopped in January 2007. Based on improvement seen in the first two cases, infliximab (3 mg/kg q 8 weeks) was initiated in March 2007 for 8

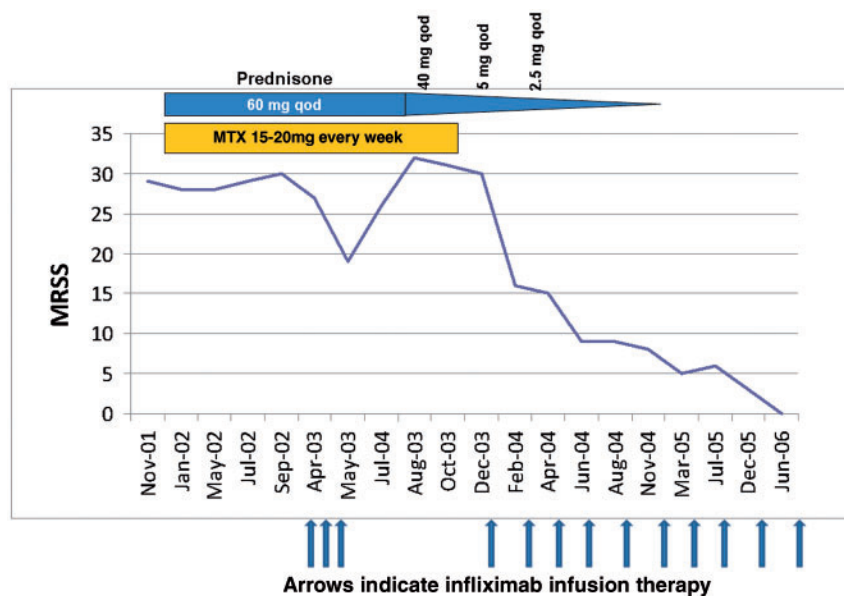
months and was stopped in October 2007. The patient noted an improvement in MRSS from 9 to 0 within 5 months. This was also associated with an increase in joint motion of the wrists and knee joints. Patient has remained in remission over the last 1.5 years with no flares.

Discussion

EF [1] is a rare fibrosing disorder that manifests as skin oedema and thickening followed by indurations. In patients with EF, histopathological findings early in the course of the disease show involvement of the deep fascia and lower subcutaneous tissue with infiltration of lymphocytes, plasma cells, histiocytes and eosinophils. Later these structures, and eventually the dermis, become thickened and sclerotic, with disappearance of inflammatory cell infiltrates. Treatment of EF usually consists of moderate- to high-dose corticosteroids. In patients who do not respond to corticosteroids, immunosuppressive agents such as MTX, ciclosporin, HCQ and PUVA phototherapy have been used.

TNF- α is a pro-inflammatory cytokine that plays an immunomodulatory role in a variety of systemic and dermatological diseases. The rationale for using anti-TNF therapy in EF comes from other rheumatic and dermatological disorders where anti-TNF therapy has been successful. Examples include RA, sarcoidosis, panniculitis, SSc, discoid LE and necrobiosis lipidica diabetorum [15]. In Crohn's disease, chronic inflammation can lead to fibrosis and scar formation [16]. In early SSc, inflammatory cells can be seen in the skin biopsy with mononuclear cell infiltrates [17]. Anti-TNF therapy has been used in SSc. In two retrospective analyses using etanercept and

Fig. 1 Disease course in Patient 2 over a period of 4 years. The y-axis represents the MRSS and arrows indicate infliximab infusions.



one small open-label study of infliximab, there were suggestions of efficacy on skin thickening and inflammatory joint involvement. However, these results are preliminary and should be interpreted cautiously [18, 19].

There have been two prior case reports documenting efficacy of infliximab therapy in EF. The first case report [20] documents a 69-year-old female initially treated with mycophenolate mofetil (2 g/day) and oral prednisone (20 mg/day) before initiating 5 mg/kg infliximab. The patient noticed an improvement in her symptoms within 1 week. The second report describes a patient with juvenile EF who presented with marked restriction of motion of his extremities and skin thickening for 3 months and he was treated with oral prednisone 2 mg/kg, pulse methylprednisone 1 g/day for 3 days and MTX 20 mg/week without much success [21]. Infliximab led to an improvement in skin thickening and laboratory parameters (normalization of acute-phase reactants and complete blood count) and the patient subsequently went into complete remission [21].

All of our patients noticed an improvement in their symptoms and skin thickening within 8 weeks of starting infliximab therapy, ultimately leading to a drug-free remission. As of November 2008, our patients have remained without therapy for their EF (range 1–3 years). No serious side effects were noted with the infliximab therapy. No MRI studies were conducted on the patients to assess treatment progression.

Our study has certain limitations. First, it is a retrospective review of three cases at a single medical centre. Secondly, MRSS has not been validated as an outcome measure in EF, although it provided us with some objective assessment in this population. A detailed description for each case of the location and quality of skin lesions before and after intervention would have been more appropriate than the MRSS. However, due to lack of any validated outcome measurement in EF, we relied on MRSS and patient-reported improvement in function. All three patients had improvement in their joint motion. Thirdly, the improvement noticed in our patients may be related to the variable natural history of EF.

These limitations notwithstanding, patients with biopsy-proven EF who have incomplete response to steroids and/or immunosuppressive medication (or become intolerant of medications and/or develop significant steroid toxicity) may achieve additional clinical benefit by initiating infliximab therapy. These data can be considered hypothesis generating for the use of anti-TNF therapy in steroid-resistant EF, and can be used as a platform to conduct a randomized controlled study to assess the efficacy of infliximab in the treatment of steroid-resistant EF.

Rheumatology key message

- Infliximab may be beneficial in patients with steroid-resistant EF.

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