CONCISE REPORT

Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients

P Efthimiou, S Schwartzman, L J Kagen

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Objective: To understand the use of tumour necrosis factor (TNF)α inhibitors in refractory dermatomyositis and polymyositis in an academic centre.

Methods: A retrospective study of eight patients with dermatomyositis or polymyositis refractory to corticosteroids and immunosuppressives who were treated with TNF inhibitors between 1998 and 2004.

Results: 8 patients with dermatomyositis or polymyositis who were treated with TNF inhibitors as adjunct treatment were identified. The mean (SD) duration of disease before initiation of TNF inhibitors was 8.5 (4.4) years. The patients failed to respond to treatment with corticosteroids (oral and intravenous); intravenous immunoglobulin and immunosuppressants (methotrexate, azathioprine, mucophenolate mofetil and leflunomide); 4.5 (1.4) immunosuppressants had been used before TNF treatment. Six patients were treated with etanercept alone, one with infliximab and one sequentially with both agents. Of the eight patients, six showed a favourable response with improved motor strength and decreased fatigue after 15.2 (6.5) months. Two of the patients did not respond after 4 (1.4) months and TNF inhibitors were discontinued. Responders showed a 54.4% (27.7%) decrease in serum concentration of creatine kinase, which was grossly abnormal (4463.5 (4036.4) U/l). Non-responders had similar reductions in creatine kinase concentration (56.1% (20.4%)), but their pre-treatment concentrations were in the normal range (118.5 (19.1) U/l).

Conclusion: Anti-TNF agents may be useful in some patients with refractory dermatomyositis or polymyositis.

Polymyositis and dermatomyositis, together with inclusion-body myositis (IBM), represent nosological forms of the rare idiopathic inflammatory myopathy (IIM) disease group, characterised by chronic, acquired skeletal muscle inflammation.[1]

Cytokines such as tumour necrosis factor (TNF)α, TNFβ, interleukin (IL)1α, IL1β, IL2 and interferon (IFN)γ were raised in muscle biopsy specimens from patients with dermatomyositis or polymyositis and may contribute to the inflammatory cascade that leads to capillary and myofibril damage.[2]

Abnormally high levels of TNFα (and β) may be toxic to existing myofibrils, while simultaneously preventing the formation of new ones.[3] An association of dermatomyositis with a −308A TNFα polymorphism has been reported.[4] Serum levels of soluble TNF receptors 1 and 2 were raised in patients with active dermatomyositis or polymyositis when compared with those in controls[5] or in patients with inactive disease.[6] Increased TNFα mRNA expression in muscle biopsy specimens was reported in some,[7 8] but not all, studies.[9]

An in vitro study showed that the p75 TNFα soluble receptor alone, or in combination with the type II, IL1β soluble receptor, attenuated IL6 production and class I major histocompatibility complex expression on the surface of myoblasts stimulated with TNFα or IL1β.[10]

Therefore, TNFα may be an attractive therapeutic target, especially in myositis resistant to conventional treatments. Published studies are limited to sporadic case reports and small series.[11–13] We report our experience with eight patients, the largest series to date.

PATIENTS AND METHODS

Patient identification

This retrospective study was based on a review of medical records from patients with dermatomyositis or polymyositis treated in our tertiary referral centre (Hospital for Special Surgery, New York, USA) between 1998 and 2004. Patients gave informed consent. Eight patients refractory to corticosteroids and disease-modifying antirheumatic drugs (DMARDs) were treated with TNF blockers, and were followed up by the same rheumatologist. Six patients fulfilled the classification criteria of Peter and Bohan[14] for definitive myositis and two patients (one with dermatomyositis and one with polymyositis who declined muscle biopsy) for probable myositis.

Anti-TNF treatment

Etanercept and infliximab were the anti-TNF agents used at doses similar to the ones used at the time for rheumatoid arthritis (ie, 3 mg/kg infusion of infliximab given at weeks 0, 2 and 6, and every 8 weeks thereafter, and 25 mg etanercept given subcutaneously twice weekly). The study required no minimal duration of treatment, and patients who had received at least one dose were included.

Efficacy and tolerance of anti-TNF treatment

Patients were followed up monthly with clinical assessment and laboratory tests, including creatine kinase, myoglobin, aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase levels in serum. Response was defined as improvement in fatigue (as reported by the patients), muscle strength (global assessment of the doctor: better or not better) and laboratory manifestations. Assessment in muscle strength included demonstrations of the following tasks by patients: climbing stairs, getting up from a deep seat and crossing legs while supine. Responders had to show improvement in the execution of all three tasks. No response was defined as the absence of noticeable improvement in 3 months after initiation of treatment. Partial response was

Abbreviations: DMARD, disease-modifying antirheumatic drug; IBM, inclusion-body myositis; IFN, interferon; IIM, idiopathic inflammatory myopathy; TNF, tumour necrosis factor

defined as the persistence of one or several myositis-related clinical manifestations. In the case of a partial response, the remaining symptoms were recorded. In the case of discontinuation of treatment, the reason for discontinuation was recorded. All side effects, suspected or certain, were also noted, as well as the interventions prompted by their appearance.

RESULTS

Eight patients (five women and three men) were identified. Three were diagnosed as having dermatomyositis and five as having polymyositis. The mean age was 58.8 (SD 14.5; median 64) years. Mean disease duration was 8.5 (4.4; median 9) years. In all, 5 (62.5%) patients had undergone muscle biopsies and 3 (37.5%) patients had electromyograms confirming the diagnosis of dermatomyositis or polymyositis. All patients had pronounced weakness and had previously failed treatment with corticosteroids (oral or intravenous bolus), intravenous immunoglobulin G (IgG) and DMARDs (methotrexate, azathioprine, mycophenolate mofetil and leflunomide). The mean number of drugs used unsuccessfully before the institution of anticytokine treatment was 4.5 (1.4). In all, 6 (75%) patients were treated with etanercept, 1 (12.5%) with infliximab and 1 (12.5%) was sequentially treated with both agents. TNF blockade was an add-on treatment, and background treatment with corticosteroids, intravenous IgG and DMARDs was continued. Intravenous IgG and DMARDs had been used for at least 3 months before patients were considered to be incomplete responders and candidates for anti-TNF treatment. In all, 7 (87.5%) patients continued to receive low doses of oral prednisone and 6 (75%) continued monthly infusions of methylprednisolone, and 2 (25%) patients were continued on methotrexate and 3 (37.5%) on azathioprine. All patients were being infused monthly with intravenous IgG (2 g/kg).

Infliximab and etanercept were both well tolerated, with few reported side effects. One patient on etanercept had recurrent oesophageal candidiasis, which was treated with fluconazole. Another patient on etanercept had frequent headaches and reappearance of Raynaud's phenomenon. A third patient developed sinus congestion, epistaxis and lightheadedness. Sinus congestion and increase in cardiac irregularity in a patient with baseline atrial fibrillation prompted the discontinuation of etanercept in a fourth patient. A splenic tumour, potentially associated with the underlying polymyositis or the use of anti-TNF treatment, prompted the discontinuation of etanercept after 20 months of use. A patient who had prior radiographic evidence of mild interstitial fibrosis experienced no difference after anti-TNF treatment.

Of the eight patients, 6 (75%) had a favourable response, with improved motor strength and decreased fatigue. The mean duration of follow-up was 15.2 (SD 6.5; median 15) months. Of the six responders, five were treated with etanercept and one was treated with both agents. A favourable treatment effect was discernible in the first 2–3 months and consisted of both clinical improvement and a decrease in serum levels of muscle enzymes. Responders showed a dramatic drop in serum levels of creatine kinase. Their highly raised pre-treatment serum concentrations of creatine kinase, with a mean of 4463.5 (SD 4036.4) U/l, quickly dropped by a mean of 54.4% (27.7%) after institution of anti-TNF. Only one patient achieved normalisation of serum creatine kinase levels after treatment, a development that was paralleled with complete clinical remission (table 1).

In all, two patients did not respond and anti-TNF agents were stopped after a mean duration of 4 (SD 1.4; median 4) months. The first non-responder was a 73-year-old man with dermatomyositis, treated with four infusions of infliximab (in conjunction with oral prednisone, pulse methylprednisolone and methotrexate), with no clinical benefit. The second non-responder was a 68-year-old man with polymyositis, on etanercept for 5 months (along with pulse methylprednisolone, azathioprine and intravenous IgG), who showed no improvement and eventually discontinued the drug because of side effects. These two non-responders had normal pre-treatment serum concentrations of creatine kinase (mean 118.5 (SD 19.1) U/l) in common, which was in sharp contrast with the responders' highly abnormal pre-treatment serum concentrations of creatine kinase (mean 4463.5 (4036.4) U/l). The mean drop in percentage for the non-responders, however, was 56.1% (20.4%), which was similar to that for the responders 54.4% (27.7%).

DISCUSSION

These findings suggest that the addition of TNFα inhibitor to standard treatment may be useful in some cases of refractory polymyositis and dermatomyositis. Both etanercept and infliximab seemed to be efficacious as adjunctive treatments in our patient group. The patients who benefited the most from anti-TNF adjunctive treatment had high serum levels of creatine kinase at baseline. Clinical improvement was paralleled by considerable reduction in the serum levels of creatine kinase during TNF inhibition.

Clinicians may consider the use of TNFα inhibitors in patients with treatment-refractory dermatomyositis or polymyositis, where standard treatment with corticosteroids, DMARDs or intravenous IgG has failed to induce and sustain remission. Serum levels of creatine kinase may guide the selection of patients for anti-TNF treatment, as we showed that patients with high creatine kinase levels, possibly indicating a more inflammatory type of disease, were more likely to benefit. Monitoring the levels of creatine kinase may also help in assessing response to treatment.

These results are consistent with those of previous reports on favourable outcomes with the use of TNF blockers in smaller series of patients with IIM. Hengstman *et al*[12] reported the results of two patients with newly diagnosed IIM (one with dermatomyositis and one with polymyositis) who were treated with infliximab (10 mg/kg every 2 weeks) alone. The increase in muscle strength correlated with improvements in serum levels of creatine kinase, electromyograms and the histological picture in post-treatment muscle biopsy specimens. In a follow-up paper, Hengstman *et al*[13] suggested that the TNF blockade may be more efficacious as rapid induction treatment, as the benefit in these two patients waned over time without the concomitant use of DMARDs. Sprott *et al*[11] reported a case of polymyositis resistant to prednisone, methotrexate and intravenous IgG and intolerant to azathioprine, whose treatment with etanercept (25 mg subcutaneously twice weekly) led to improved strength and the discontinuation of prednisone.[11] In another report, etanercept treatment of four refractory patients with dermatomyositis or polymyositis resulted in decreased levels of creatine kinase, prednisone tapering and increased muscle strength in two of the four patients.[15]

Our study has several limitations because of its retrospective design and lack of standardised outcome measures. Muscle biopsy specimens before and after treatment were not obtained. It is possible that, in those three patients who did not undergo a muscle biopsy, the diagnosis of myositis was made erroneously, as some rare genetic myopathies can occasionally mimic myositis. A longer follow-up would be necessary to show a disease-modifying versus a remission–induction effect.

Despite these limitations, many of which are inherent in retrospective research, we believe that our real-life experience

Table 1 Evolution of patients with DM or PM on anti-TNF treatment

Patient number	Sex	Age (years)	DM/PM	Duration of DM/PM (years)	Drugs tried before anti-TNF treatment	Pre-treatment CK (U/l)	Anti-TNF agent	Concurrent drugs	Post-treatment CK (U/l)	Clinical response	Follow-up
1	F	33	PM	10	PDN, IVM, IVIG, AZA, MTX	9959	Etanercept 25 mg biw	PDN, IVM, IVIG, AZA, MTX	7905	Improved	At 9 months still on etanercept
2	F	44	DM	3	PDN, IVM, IVIG, AZA, MTX	4380	Etanercept 25 mg biw	PDN, IVM, IVIG, MTX	69	Improved	D/C etanercept after 8 months because she felt better.
3	F	41	PM	7	PDN, IVM, IVIG, AZA, MTX, MMF	1996	Etanercept 25 mg biw	PDN, IVIG, AZA	1164	Improved	D/C etanercept after 2 months because of candida esophagitis.
						5489			4584		At 12 months still on etanercept; recurrent esophagitis treated with fluconazole.
4	F	41	DM	2	PDN, IVM, IVIG, MTX	3198	Infliximab 3 mg/kg	PDN, IVIG, MTX	5311	Partial response	Worsened after 3 infusions.
						5311	Etanercept 25 mg biw		2214		Improved after 3 months treatment. Self D/C because of sinus problems.
						8772	Infliximab 3 mg/kg		4508		Restarted on remicade and improved; D/C after 14 months→ lost efficacy.
5	M	73	DM	13	PDN, IVM, IVIG, AZA, MTX, LEF	132	Infliximab 3 mg/kg	PDN, IVM, IVIG, MTX	77	No benefit	D/C infliximab after 4 infusions.
6	M	68	PM	11	PDN, IVM, IVIG, AZA, MTX	105	Etanercept 25 mg biw	PDN, IVM, IVIG, AZA, MTX	31	No benefit	D/C etanercept after 5 months; complications: nasal congestion, cardiac irregularity.
7	M	60	PM	14	PDN, IVM, IVIG, AZA	1224	Etanercept 25 mg biw	PDN, IVM, IVIG	700	Improved	At 24 months still on etanercept.
8	F	70	PM	8	PDN, IVM, IVIG, AZA, CY	450	Etanercept 25 mg biw	PDN, IVM, IVIG	270	Improved	D/C etanercept s/p 20 months when splenic tumour/ascites were diagnosed.

AZA, azathioprine; biw, twice weekly; CK, creatine kinase; CY, cyclophosphamide; D/C, discontinued; DM, dermatomyositis; F, female; IVIG, intravenous immunoglobulin G; IVM, intravenous methylprednisolone; LEF, leflunomide; M, male; MMF, mycophenolate mofetil; MTX, methotrexate; PDN, prednisone; PM, polymyositis; TNF, tumour necrosis factor

suggests a possible therapeutic role for TNF inhibitors, which can be proved only with randomised controlled studies using standardised efficacy measures.[16] Until then, TNF blockade may be judiciously used as an adjunct treatment in refractory cases in which other conventional treatments have failed.

Authors' affiliations

P Efthimiou, Division of Allergy, Immunology, and Rheumatology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, New Jersey, USA
S Schwartzman, L J Kagen, Department of Medicine, Hospital for Special Surgery, New York, USA; New York Presbyterian Hospital, Weill Medical College of Cornell University, New York

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Correspondence to: P Efthimiou, 90 Bergen Street, DOC#4700, Newark, NJ 07103, USA; efthimpv@umdnj.edu

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