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# Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients

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***Objective*. To assess the effects prospectively of tumour necrosis factor (TNF) receptor superfamily (TNFRSF) fusion proteins TNFRSF1B (etanercept) and TNFRSF1A (p55TNFr-Ig) in patients with TNF receptor associated periodic syndrome (TRAPS).**

***Methods*. Seven patients with a clinical and genetic diagnosis of TRAPS received subcutaneous etanercept for 24 weeks. One of these patients had previously received an intravenous infusion of p55TNFr-Ig. Therapeutic response was assessed by comparing corticosteroid requirement, acute-phase response and an established scoring system over 20 weeks, both on and off etanercept.**

***Results*. Etanercept was well tolerated. The five corticosteroid-responsive patients required significantly less corticosteroids and demonstrated reductions in acute-phase reactants on etanercept. The two patients not requiring corticosteroids had small reductions in disease activity scores. The effect of p55TNFr-Ig in a single patient with TRAPS remains unclear.**

***Conclusions*. Etanercept does not abolish inflammatory attacks but improves disease activity allowing corticosteroid reduction. Etanercept may be clinically useful in replacing or reducing steroid requirements in the treatment of TRAPS. A formal trial of etanercept to establish its role in clinical management is indicated.**

KEY WORDS: Tumour necrosis factor associated periodic syndrome, Etanercept, p55TNFr-Ig.

Tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) is a rare autoinflammatory, autosomal dominantly inherited condition characterized by recurrent fevers, rashes and musculoskeletal problems associated with missense mutations of the 55 kDa tumour necrosis factor receptor superfamily 1A (TNF-receptor 1) [1, 2]. Variability among patients in age of disease onset and frequency, length and severity of inflammatory attacks is characteristic. TRAPS may be difficult to treat with patients experiencing significant pain and disability. Inflammatory attacks may respond to corticosteroids in some patients such that they require large and frequent doses, for example 40 mg of prednisolone daily, with the associated morbidity. We have previously treated TRAPS patients with immunomodulators including azathioprine, methotrexate, cyclosporin, tacrolimus, cyclophosphamide and thalidomide without clear benefit. A few patients may gain some symptomatic

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relief from colchicine and high-dose non-steroidal anti-inflammatory drugs. In addition TRAPS may be complicated by amyloidosis, emphasizing the need to search for novel treatment strategies [2, 3]. The molecular mechanisms resulting in flares of TRAPS are currently unknown although aberrant signalling through TNF receptors may be central to the autoinflammatory process [4, 5]. We studied the use of TNFRSF1A and TNFRSFIB fusion proteins in an open label series. TNFRSF1A agents remain in development, whilst the beneficial role of etanercept in inflammatory disease such as rheumatoid arthritis and juvenile chronic arthritis is well established [6, 7].

## Patients and methods

### *Etanercept*

The entry criteria for etanercept treatment were patients with a clinical and genetic diagnosis of TRAPS who were (i) requiring frequent courses of corticosteroids (patients 1–5) or (ii) having symptoms not responding to oral corticosteroids (patients 6–7), with all patients having symptoms including pain and disability, interfering with daily activities. Etanercept was given as a 25 mg subcutaneous dose twice weekly for 24 weeks. Patient 1 having received p55TNFr-Ig underwent two consecutive cycles both on and off etanercept. Patients received no concurrent immunosuppressive treatment except for corticosteroids for at least 3 months prior to starting etanercept or during the study periods. The patients known to respond to corticosteroids were instructed to use oral prednisolone as required both whilst on and off etanercept therapy. Severe attacks that did not respond to at least 40 mg of oral prednisolone per day were treated with 500–1000 mg i.v. methylprednisolone infusions. All results in the first 4 weeks after starting and stopping etanercept were excluded from analysis. Daily corticosteroid dose was documented and total dose calculated over each 20-week period. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured on venous blood at a minimum of every 5 weeks throughout the study with the exception of patient 7 (see below). In addition, some patients had CRP and ESR measured during inflammatory attacks, which was consistent within each patient whilst on and off etanercept therapy. Median CRP and ESR values (incorporating at least four values on and off treatment) were calculated and a range expressing highest and lowest values noted. Patients were invited to record daily scores for both general well-being and pain and stiffness in a validated patient diary card where a score of 100% represented maximal well-being or no pain and stiffness. Daily oral temperature was documented in patient 1. Possible side-effects related to etanercept were noted.

### *p55TNFr-Ig treatment in patient 1*

He was treated with a single 100 mg i.v. infusion of a p55TNFr-Ig chimeric molecule containing the extracellular domain of the human TNFRSF1A coupled to the hinge CH2 and CH3 constant regions of human IgG1 heavy chain (gift from Professor H. Waldmann and Dr G. Hale, Oxford Therapeutic Antibody Centre). The patient had received no immunosuppressive agents except corticosteroids in the 3 months prior to p55TNFr-Ig and was given an infusion of p55TNFr-Ig on the fourth day of an acute attack of TRAPS. The patient had discontinued corticosteroids to facilitate assessment of benefit due to p55TNFr-Ig. Acute-phase response and corticosteroid use was documented for 3 months prior to and after p55TNFr-Ig.

### *Patient details*

Patient 1 was a 48-yr-old male with a C33Y TNFRSF1A mutation (C33Y TRAPS) with recurrent episodes of fevers, myalgias, lymphadenopathy, ptosis, migratory erythematous rash, arthralgia, and chest and abdominal pain since 2 yr of age. Over the last 7 years his condition had deteriorated with increasing frequency and severity of attacks resulting in regular high-dose corticosteroid use. His persistent poor health had resulted in him being unable to sustain regular employment. Previous treatments including oral azathioprine, methotrexate, cyclosporin, thalidomide and i.v. cyclophosphamide gave no benefit. He initially received i.v. p55TNFr-Ig. Following p55TNFr-Ig therapy he was found to have developed hypoadrenalism, presumed secondary to prolonged corticosteroid use, and thereafter received at least 5 mg of prednisolone daily. Following a 3-month washout period he underwent two repeat cycles of 24 weeks on and off etanercept. A subsequent course of two doses of i.v. infliximab at 5 mg/kg was unhelpful.

Patient 2 was a 25-yr-old female with C33Y TRAPS with fever, abdominal pain and vomiting since 18 months of age, regularly requiring 20–30 mg of prednisolone daily. In May 1999, her TRAPS became complicated by the development of nephrotic syndrome and a serum amyloid P (SAP) scan confirmed type AA amyloidosis [3].

Patient 3 was a 55-yr-old male with C33Y TRAPS characterized by abdominal pain, myalgias and rashes approximately every 6 weeks. Previous unsuccessful treatments included colchicine, azathioprine, cyclosporin and thalidomide.

Patient 4 was a 33-yr-old female with C33Y TRAPS comprising fevers, myalgias and rash requiring intermittent, albeit frequent, doses of oral prednisolone. This was associated with persisting anaemia and high acute-phase response. The birth of her first child created increased problems with activities of daily living such as lifting. Her attacks had not been improved by colchicine, i.v. immunoglobulin, cyclosporin or tacrolimus.

Patient 5 was a 31-yr-old female with C33Y TRAPS since 20 yr of age and has had regular attacks with fever, abdominal pain, myalgia and lymphadenopathy. Colchicine produced no benefit and was withdrawn owing to gastrointestinal side-effects and cyclosporin resulted in unacceptable hirsutism.

Patient 6 was a 37-yr-old male with R92Q TRAPS. At the age of 29 yr he developed severe attacks of fevers, rigors and abdominal pain recurring every few years. Other frequent symptoms have included calf pain, breathlessness, testicular pain, fatigue and the development of a rash for the first time at 37 yr. He was unresponsive to corticosteroids including a trial of three 1000 mg methylprednisolone infusions. CRP and ESR were often normal during symptomatic attacks.

Patient 7 was a 5-yr-old boy with R92Q TRAPS since 1 yr of age and has suffered with frequent febrile attacks with abdominal pain, diarrhoea, vomiting, conjunctival injection, ptosis, calf pain and lymphadenopathy. His symptoms are not steroid responsive. Owing to problems with venesection, CRP only was measured five times on etanercept and on three occasions off treatment.

### *Statistical analysis*

Corticosteroid use in 20-week periods on and off etanercept in C33Y TRAPS (all corticosteroid-responsive patients) was

compared using the Wilcoxon Pair Signed Rank test. The Mann–Whitney test (two-tailed) was used to compare ESR and CRP values in study periods on and off etanercept for C33Y TRAPS, and also for patient scoring systems in all patients. All tests were performed by SPSS.

## Results

### *Etanercept*

All seven patients completed 24 weeks of etanercept therapy and no serious adverse events or hospital admissions were reported. Only minor injection site reactions and in patient 5 upper respiratory tract infections were noted whilst on etanercept. Corticosteroid requirements (Table 1) were reduced during etanercept treatment in all five steroid-responsive patients giving a Wilcoxon Signed Rank Test value of $P = 0.028$. No severe attacks requiring methylprednisolone infusions occurred during treatment with etanercept. Patient 1 required less corticosteroids on etanercept during both cycles although this was more marked during cycle 1.

CRP and ESR were reduced in patients 1–5 whilst on etanercept and this reached statistical significance for three out of the five C33Y TRAPS patients (Mann–Whitney test) (Table 2). The acute-phase response did not rise for patients 6 and 7 during exacerbations of inflammatory symptoms when compared with regular monitoring.

All patients completed daily scores whilst on etanercept although scores are incomplete for two patients whilst off treatment (Table 3). Patient 3 demonstrated the greatest difference in scores with 91 and 90% on etanercept compared with 71 and 67% off treatment for general well-being, and pain and stiffness, respectively. Six out of the seven patients showed a significant difference in either or both of the two scoring systems.

Patient 1 reported 16 and 18 days with fever of at least 37.5°C whilst on etanercept compared with 13 and 39 days with fever off treatment for the two treatment cycles. Patient 2 developed an unanticipated remission of her nephrotic syndrome as previously reported [3].

### *p55TNFr-Ig treatment*

Patient 1 received p55TNFr-Ig (day 1) on the fourth day of a flare of TRAPS comprising fevers maximally up to 38.8°C and myalgia. No side-effects were apparent although his attack continued with fevers, rigors, sweating, myalgia, conjunctivitis, nausea and abdominal pain. On days 4 and 5 he received 30 mg of oral prednisolone daily without benefit. On day 6 his severe and persisting symptoms were improved by a 1000 mg methylprednisolone infusion. Three days later, however, he developed further myalgia and abdominal pain and commenced 35 mg of oral prednisolone daily. Oral prednisolone was reduced over the next 8 weeks to 10 mg daily whilst he described less severe but continued myalgia and abdominal pain. After 1 week on 10 mg of

Table 1. Corticosteroid use in 20-week study period on and off etanercept in C33Y TRAPS

| Patient | Total mg of prednisolone on etanercept | Total mg of prednisolone off etanercept | Total mg of methylprednisolone on etanercept | Total mg of methylprednisolone off etanercept |
|---|---|---|---|---|
| 1 (cycle 1) | 1303 | 3145 | 0 | 2000 |
| 1 (cycle 2) | 2595 | 3141 | 0 | 1000 |
| 2 | 20 | 1430 | 0 | 0 |
| 3 | 0 | 352 | 0 | 0 |
| 4 | 275 | 745 | 0 | 0 |
| 5 | 120 | 514 | 0 | 0 |

Wilcoxon Pair Signed Rank test for comparing prednisolone use on and off etanercept = 0.028.

Table 2. Acute-phase response comparing 20-week study periods on and off etanercept

| Patient | Median CRP on etanercept | Median CRP off etanercept | Mann–Whitney test for CRP | Median ESR on etanercept | Median ESR off etanercept | Mann–Whitney test for ESR |
|---|---|---|---|---|---|---|
| (a) C33Y TRAPS | | | | | | |
| 1 (cycle 1) | 9.5 (3–162) | 28 (3–139) | 0.160 | 30 (10–90) | 34 (11–90) | 0.281 |
| 1 (cycle 2) | 24 (5–103) | 41 (6–156) | 0.587 | 40.5 (11–80) | 31.5 (13–81) | 0.846 |
| 2 | 3 (3–18) | 6 (4–82) | 0.012 | 62 (32–84) | 92 (38–100) | 0.042 |
| 3 | 13 (7–41) | 135 (49–151) | 0.009 | 30 (16–59) | 87 (72–100) | 0.009 |
| 4 | 144 (125–204) | 151 (97–216) | 0.806 | 89 (68–100) | 97 (38–100) | 0.453 |
| 5 | 3 (3–3) | 16 (8–26) | 0.004 | 3 (3–9) | 21 (13–27) | 0.010 |
| (b) R92Q TRAPS | | | | | | |
| 6 | 4 (3–4) | 4 (4–4) | – | 3.5 (3–4) | 3 (3–3) | – |
| 7 | 5 (3–9) | 5 (5–7) | – | | | – |

In patient 7, CRP off etanercept incorporates 3 values (see text). CRP = mg/l; ESR = mm/h.

TABLE 3. Average patient recorded symptom scores during 20-week study periods on and off etanercept

| Patient | Average score well-being on etanercept (%) | Average score well-being off etanercept (%) | Mann–Whitney test well-being | Average score pain and stiffness on etanercept (%) | Average score pain and stiffness off etanercept (%) | Mann–Whitney test pain and stiffness |
|---|---|---|---|---|---|---|
| (a) C33Y TRAPS | | | | | | |
| 1 (cycle 1) | 89 | 74 | 0.004 | 89 | 76 | 0.014 |
| 1 (cycle 2) | 71 | 61 | 0.129 | 73 | 64 | 0.115 |
| 2 | 99 | 86 | <0.001 | 99 | 91 | <0.001 |
| 3 | 91 | 71 | <0.001 | 90 | 67 | <0.001 |
| 4 | 71 | 77 | 0.402 | 65 | 64 | 0.493 |
| 5 | 97 | 80 | <0.001 | 93 | 74 | <0.001 |
| (b) R92Q TRAPS | | | | | | |
| 6 | 70 | 63 | 0.047 | 75 | 67 | 0.028 |
| 7 | 82 | 75 | 0.093 | 82 | 72 | 0.018 |

Patient 2 and 6 scores off etanercept average over 5 and 10 weeks, respectively (see text).

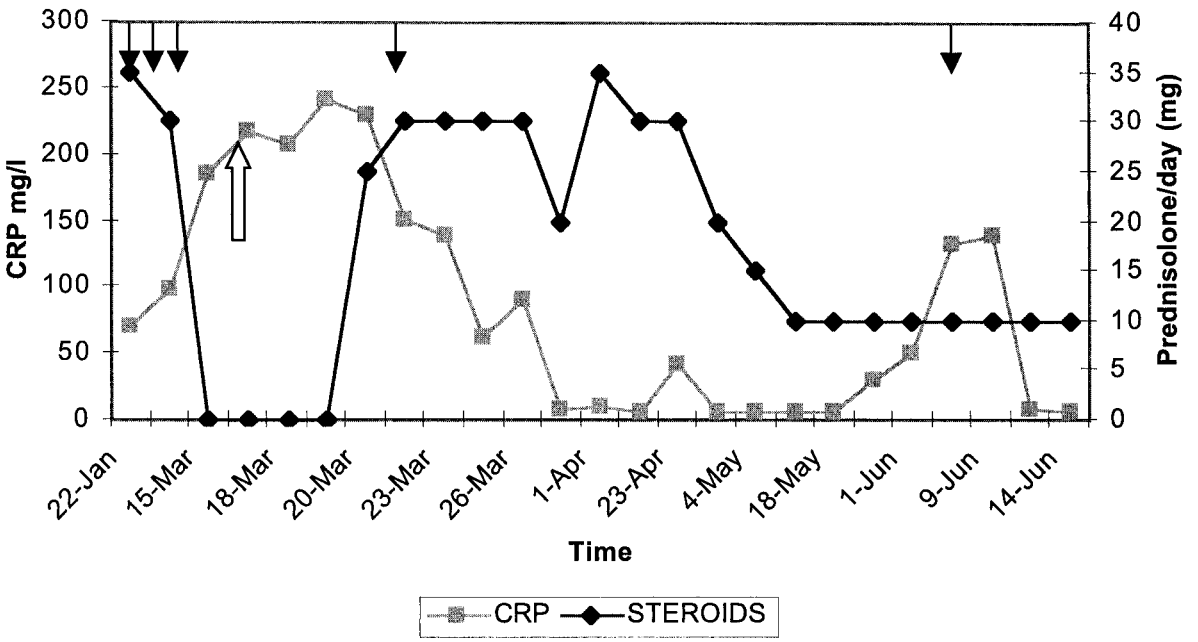


FIG. 1. Patient 1 and p55TNFr-Ig treatment. ⇧=p55TNFr Ig infusion; ↓=1 g methylprednisolone infusion.

prednisolone daily (11 weeks after p55TNFr-Ig), he developed a further flare of TRAPS. His acute-phase response reflected his clinical attacks with a CRP of 242 mg/l and ESR >100 mm/h peaking on day 3 (Fig. 1).

## Discussion

The identification of TNFRSF1A mutations as the genetic cause of TRAPS coincided with the wider use of biological agents and facilitated new treatment possibilities. This is the first reported case series examining the safety and effects of etanercept and p55TNFr-Ig in TRAPS.

Etanercept appears to be safe in the short term in TRAPS. We have also demonstrated significantly reduced corticosteroid use in the five C33Y TRAPS patients with etanercept. Response to etanercept was harder to assess in the two R92Q TRAPS patients not using corticosteroids.

Any study of a periodic fever syndrome is problematic owing to its low prevalence and the unpredictable frequency and severity of attacks. A 24-week interval on etanercept was selected to enable inclusion of patients with differing attack frequencies. Patient 1 demonstrated marked differences in corticosteroid use on etanercept during cycle 1 and 2. This could reflect fluctuation in disease activity, although declining responsiveness to etanercept over time cannot be excluded. This case series evaluated corticosteroid intake that may conceivably alter natural history of disease and hence affect scoring systems, acute-phase response and days of fever. The clinical need for methylprednisolone, only off etanercept, could mask greater differences between these parameters on and off treatment.

The availability of a p55TNFr-Ig fusion protein for patients with a mutation in this receptor resulted in us initially giving a single infusion of p55TNFr-Ig to our most severely affected TRAPS patient. The p55TNFr-Ig infusion appeared well tolerated, although administration during an attack could potentially mask side-effects. Following p55TNFr-Ig treatment the patient continued with one of his severest attacks of TRAPS. The subsequent finding that he had become steroid dependent raises the possibility that this attack could have been exacerbated or even precipitated by discontinuation of corticosteroids immediately prior to the p55TNFr-Ig infusion. Once the patient was established on permanent oral corticosteroids (day 10 onwards), he continued to experience TRAPS-related symptoms. Figure 1 suggests improvement in CRP following the resolution of the initial severe attack, although these results need to be interpreted in the context of concurrent corticosteroid use. A single infusion of p55TNFr-Ig may improve symptoms for up to 8 weeks in rheumatoid arthritis (unpublished data J.D. Isaacs). The p55TNFr-Ig could therefore have provided some benefit to this patient in weeks 2–10 when corticosteroid withdrawal was not a complicating factor. The effect of p55TNFr-Ig given during an acute attack of TRAPS is inconclusive and p55TNFr-Ig has also not been studied on a prophylactic basis in TRAPS.

This small case series reflects severe TRAPS, with p55TNFr-Ig being assessed in our most severely affected patient. The use of p55TNFr-Ig could be considered for other patients with TRAPS, although possibly using prophylactic administration. Our data demonstrating reduction in corticosteroid use support the use of etanercept in TRAPS. This could be of great value to patients who have failed with multiple immunosuppressive strategies. Different TNFRSF1A mutations may affect treatment response, but a larger study is warranted to assess the place of etanercept in the treatment of TRAPS.

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