Published in final edited form as:

Arthritis Rheum. 2012 March ; 64(3): . doi:10.1002/art.33416.

Efficacy of Etanercept in the Tumor Necrosis Factor Receptor–Associated Periodic Syndrome (TRAPS)

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Abstract

Objective—To investigate the efficacy of etanercept in improving the symptoms and underlying inflammation in patients with the TNF receptor-associated periodic syndrome (TRAPS).

Methods—Fifteen patients with TRAPS were enrolled in a prospective, open-label, dose-escalation study. Patients recorded attacks, symptom severity, and use of ancillary medications in a daily diary. Blood samples were collected during each period and measured for acute phase reactants. 7–9 years after the conclusion of the initial study, patients completed a follow-up survey and were evaluated to determine the long-term outcome of etanercept treatment.

Results—Etanercept treatment significantly attenuated the total symptom score, as well as reduced the frequency of symptoms. Etanercept also reduced acute phase reactants, particularly during asymptomatic periods. During a ten-year follow-up period, patients remained on etanercept for a median of 3.3 years, with a number of patients switching to anti-IL-1 β therapy or remaining off biologic agents, citing injection reactions and lack of efficacy most frequently for discontinuation. However, patients remaining on etanercept had reduced symptoms at follow-up.

Conclusion—Etanercept reduces symptoms and serum inflammatory markers of TRAPS in a dose-dependent manner, but does not completely normalize symptoms or acute phase reactants. Although long-term adherence to etanercept is poor, remaining on etanercept may provide continued symptomatic benefit.

INTRODUCTION

Tumor necrosis factor (TNF) plays critical roles in inflammation and immunity. TNF is implicated in the pathogenesis of rheumatoid arthritis and Crohn's disease, and TNF

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The authors declare no financial conflicts of interest.

blockade is an effective treatment in these conditions (1). TNFR1 is believed to mediate most of the pro-inflammatory effects of TNF. The autosomal dominant periodic fever syndrome TNF receptor–associated periodic syndrome (TRAPS) is associated with heterozygous missense mutations in the extracellular domain of the gene encoding TNFR1 (2). TRAPS is an autoinflammatory disease characterized by recurrent episodes of fever accompanied by abdominal pain, migratory rash, myalgia, conjunctivitis, and arthralgias lasting from a few days to several weeks (3, 4). Although attacks are usually unprovoked, patients report triggers such as stress, trauma, exercise and hormonal changes. Acute phase proteins are elevated during attacks and also during asymptomatic periods. Chronic elevation in serum amyloid-A (SAA) can result in amyloidosis and life-threatening organ damage.

Although initial studies suggested that inflammation in TRAPS might stem from reduced shedding of mutant TNFR1 from the cell surface (2), TNFR1 mutant proteins associated with TRAPS do not bind TNF. They are retained and accumulate in the endoplasmic reticulum, most likely as a result of protein misfolding, and are termed structural mutants (5). Two rare polymorphisms in the TNFR1 gene, R92Q and P46L, have also been associated with TRAPS, but behave normally in cell biological assays and lead to a less severe phenotype without progression to amyloidosis (6). Cells harboring heterozygous TNFR1 mutants exhibit increased responsiveness to TLR ligands in a manner dependent on the wild-type TNFR1, MAP kinases, and mitochondrial reactive oxygen species (7, 8). The dependence of hyper-inflammatory responses in TRAPS on interactions between TNF and the wild-type TNFR1 creates a rationale for TNF blockade in TRAPS.

Before the discovery of the genetic lesion in TRAPS, patients were treated mainly with NSAIDs and/or corticosteroids. Colchicine is not an effective treatment for TRAPS. Case reports on the use of etanercept, a fusion protein of the extracellular domain of TNFR2 and the Fc portion of human IgG1, have found variable results in TRAPS patients and rely primarily upon subjective patient reporting (4, 9, 10). Reports of the use of IL-1 β receptor antagonist anakinra and tocilizumab, which targets the IL-6 receptor, in TRAPS patients have been limited but encouraging (7, 11, 12).

PATIENTS AND METHODS

Patients

Fifteen patients were enrolled, all with features typical of TRAPS, including abdominal pain, myalgia, arthralgia/arthritis, rash, and ocular involvement during attacks, a genetically confirmed mutation in *TNFRSF1A* associated with TRAPS, and age $\geq$ 4 years (Supplemental Table 1). A minimum of two attacks during the initial 12-week period was required for inclusion. Patients were screened for TB and those with a positive PPD were excluded from the study. Protocol 94-HG-0105 is registered in clinicaltrials.gov as NCT00001373.

Study Design

Patients in the protocol were assigned to equal periods (12 to 14 weeks) of: (1) baseline observation, (2) etanercept (25 mg for adults and 0.4 mg/kg for children) twice weekly, (3) etanercept three-times weekly if there was evidence of inflammation during period 2, and (4) drug washout.

Patients recorded the frequency, duration, and severity of five TRAPS-related symptoms using an analog scale from 0 to 10 (10 being the most severe), and use of ancillary anti-inflammatory medications (i.e., NSAIDs and oral corticosteroids) in a standardized daily diary. At the conclusion of each study period, patients completed a questionnaire

quantifying pain and ancillary medication use during attacks. Serum inflammatory markers were measured during attacks and intercritical periods.

Primary outcome measures were a change in self-reported symptoms, standardized by summing the daily symptom scores in each period and dividing by the number of weeks in the respective period, and a change in mean acute phase reactants, obtained during symptomatic and asymptomatic time points in each period. A secondary outcome was the use of ancillary medications for pain relief during each period. Between seven and nine years after the initial study, patients completed the questionnaire and an oral survey to determine treatment, satisfaction with response, and medical history. Patients were then followed prospectively for the remainder of the ten-year follow-up period. Serum SAA levels were determined from patient serum using a commercially available ELISA kit (Antigenix America, Inc.) as per the manufacturer's protocol. CRP and ESR were determined by the NIH clinical laboratory.

Statistical Analysis

Statistical analyses were performed with Prism 5 software (GraphPad Software, Inc.). For symptom scores, symptom-free days, and questionnaire data, statistical significance was determined by a paired Student's *t* test, except for comparison of groups of patients off and on etanercept in the follow-up study. For the biochemical studies, statistical significance was determined using the Wilcoxon signed rank test. All statistical tests were two sided, and *P* values less than 0.05 were considered statistically significant.

RESULTS

Thirteen of the fifteen patients initially enrolled completed the treatment trial (Supplemental Table 1, Supplemental Figure 1). Etanercept was well tolerated by all participants, with the most commonly reported adverse effect being localized injection-site reactions. There were no serious adverse events reported throughout the course of the study. Each of the participants that completed period 2 required an increase in the dosing of etanercept to three times per week. Twice weekly (period 2) and three-times weekly (period 3) etanercept administration were significantly associated with a dose-related attenuation in the total symptom score, decreasing by 36% ($P = 0.02$) in period 2 and 66% ($P < 0.0001$) in period 3 (Figure 1A). Symptoms rapidly increased after a drug washout in period 4 as compared with period 3 ($P = 0.0006$), occurring on average within 3.3 weeks after discontinuation of etanercept. Analysis of individual patient responses revealed that all patients experienced a decrease in total symptom scores, with the patients having the highest initial symptom scores often experiencing the largest decreases (Supplemental Figure 2A). The mean number of symptom-free days per week as recorded in the daily diaries increased significantly to 3.2 ($P = 0.006$) and 4.3 ($P = 0.0008$) days per week in periods 2 and 3, respectively, as compared with 1.4 in period 1 (Figure 1B). Additionally, the mean number of symptom-free days per week significantly decreased to 2.4 days ($P = 0.002$) after the discontinuation of etanercept in period 4 as compared with period 3. When responses of individual patients were analyzed, symptom free days increased in most patients (Supplemental Figure 2B). Nevertheless, TRAPS-associated symptoms were still being reported even at the higher dose of etanercept. Individual symptoms also decreased during etanercept treatment in concordance with the total symptom score, with significant decreases in all symptoms during period 3, except for ocular manifestations, which were less prominent in this cohort and not significantly affected in either period 2 or 3 (Figure 1C).

When measured during asymptomatic periods, all three measures of acute phase reactants were significantly lower during etanercept treatment (Figure 2A–C), and returned to baseline during period 4. Individual patients with the highest CRP values did show the most

dramatic declines with etanercept (Supplemental Figure 2C). Interestingly, laboratory values measured during flares were much less affected, with a trend towards reduction in CRP and SAA levels during attacks with etanercept therapy in periods 2 and 3 but no discernable change in ESR (Figure 2D–F). The maximum and average pain score during attacks declined significantly during etanercept treatment, and use of ancillary medications (NSAID and glucocorticoids) declined accordingly (Figure 3A, B). This paralleled the daily diary results, in which use of NSAIDs declined by 41% and 88% in periods 2 and 3, respectively, compared to baseline, with a rebound during period 4.

Patients who completed the initial study were re-evaluated between seven and nine years after its conclusion, and all were followed thereafter until ten years following the initial study. The median self-reported duration of etanercept treatment over the ten-year period was 3.3 years, with the most common reasons for discontinuation of etanercept being a perceived lack of efficacy and injection site reactions (Figure 3C). During the follow-up period, 6 patients received anakinra and all experienced clinical benefit. However, 4 patients discontinued the treatment because of painful site reactions. The 2 patients remaining on anakinra reported sustained improvement of their symptoms. Importantly, those patients on etanercept experienced less pain during attacks compared to those not on etanercept (Figure 3A). However, this did not seem to limit their use of NSAIDs or corticosteroids, which were comparable between those on and off etanercept, as well as higher than during the initial study (Figure 3B).

DISCUSSION

These results represent the largest prospective clinical trial of etanercept in TRAPS. The observation that laboratory and clinical parameters improved during treatment with etanercept suggests that primary or secondary TNF-dependent signaling is an important component of the pathogenesis of TRAPS. Our findings are consistent with results in animal models of TRAPS, in which inflammation is partially dependent on TNF. Sustained increases in SAA above 10 mg/L are associated with the development of amyloidosis (13), and suppression of SAA below this level was achieved in most patients at the higher dose of etanercept. However, we could not assess the ability of etanercept to prevent amyloidosis, as no study patients developed this complication.

Despite the overall beneficial effects of etanercept, the majority of patients discontinued etanercept during the open-label follow-up period, with a median time remaining on therapy shorter than has been observed in open-label extensions of controlled trials of other rheumatic diseases (14, 15). Perceived lack of efficacy was the most common reason for discontinuation of etanercept therapy. This may reflect the inability of etanercept to fully control the symptoms of TRAPS, and is in agreement with other reports of variable efficacy of etanercept in TRAPS (10). The second most common reason for discontinuation of etanercept was painful injection site reactions (6 of 13 patients; 46%). As skin manifestations are common in TRAPS, it is possible that the high rate and severity of injection site reactions could be related to the disease. The low numbers of patients who continued on etanercept during the follow-up period may also reflect the less controlled setting of the follow-up period compared to the initial structured treatment trial, medication availability, and/or cost. It is also possible that although TNF is important in the pathophysiology of TRAPS, other cytokines become more important over time. This is consistent with observations of clinical improvement in TRAPS symptoms after anakinra administration in patients who were refractory to TNF blockade (7, 11).

Despite the relatively low adherence to etanercept therapy during the long-term follow-up period, patients continued to experience a reduction in the severity of attacks, as measured

by the attack pain score. Two patients restarted etanercept after a number of years off therapy and still reported a therapeutic benefit (Figure 3, patients 6 and 7). Etanercept appears to be well tolerated and safe at the doses used in this study, and we recommend that etanercept continue to be used in this disease. Short-term, the efficacy of etanercept in TRAPS seems clear, and patients continue to experience clinical benefit over a long-term follow-up period. Only one patient with a *SNP*-related TNFR1 variant (P46L) completed the study, and further studies of patients with these variants are needed. Treatment aimed at blocking other cytokines or intracellular mediators of inflammation such as reactive oxygen species (8) may help to obtain better control of the symptoms and autoinflammation in TRAPS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the clinical staff of NIAMS, particularly Jane Dean, Anne Jones, Beverly Barham, Dr. Amanda Ombrello, and Dr. Karyl Barron (NIAID), for excellent patient care and research support. Ariel Bulua, Douglas Mogul, and Harjot Singh were trainees in the NIH Clinical Research Training Program, a public-private partnership between the NIH and Pfizer, Inc.

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Figure 1. Effect of etanercept on symptom scores and symptom-free days in TRAPS

Average weekly symptom scores (A) and symptom-free days per week (B) were measured in TRAPS patients (n=14) over the four study periods. Individual symptom scores (rash, eye redness/swelling, abdominal pain, muscle pain, and joint pain) are shown (C). Symptom score is from 0–10; 10 is most severe, 0 is least. P = period. Error bars represent mean ± SEM. *, $p < 0.05$; **, $p < 0.01$, relative to period 1. ‡, $p < 0.05$; ‡‡, $p < 0.01$, relative to period 3.

Figure 2. Reduction in serum acute phase reactants with etanercept therapy in TRAPS

CRP, SAA, and ESR levels were measured in TRAPS patients (n=14) during asymptomatic periods (A, B, C) and during attack periods (D, E, F) over the four study periods. The box limits represent 25th and 75th percentiles, the line within the box shows the median, and the whiskers end at 1st and 99th percentiles. P = period. *, p < 0.05; **, p < 0.01, relative to period 1. ‡, p < 0.05; ††, p < 0.01, relative to period 3.

Figure 3. Biologic therapy decreases attack severity in the short- and long-term

Maximum and average attack-associated pain scores (A) and attack ancillary anti-inflammatory medication use (B) were recorded at the conclusion of each study period (n=14) and at the long-term follow-up (off etanercept, n=10; on etanercept, n=4). Pain score is from 0–10; 10 is most severe, 0 is least. Ancillary medication use is scored from 0–3; 3 is most use, 0 is least. (C) TRAPS patient medication use over a ten-year follow-up period is shown. Letters correspond to reason for discontinuation of etanercept therapy. *, time of completion of study questionnaire (patient 6 and 7 completed questionnaire twice). GC PRN = corticosteroids as needed. P = period. Error bars represent mean $\pm$ SEM. *, $p < 0.05$; **, $p < 0.01$, relative to period 1. †, $p < 0.05$, relative to period 3. ††, $p < 0.01$, relative to off etanercept at follow-up.