Mod Rheumatol (2010) 20:561–565
DOI 10.1007/s10165-010-0320-8

ORIGINAL ARTICLE

Etanercept response in patients with rheumatoid arthritis after secondary loss of efficacy of infliximab

Hiroaki Matsuno

Received: 17 February 2010 / Accepted: 11 May 2010 / Published online: 16 June 2010

Abstract This study was carried out to determine the effectiveness of half-dose administration of etanercept in patients with rheumatoid arthritis (RA) who exhibited secondary loss of efficacy of infliximab. Seventeen patients were administered 25 mg of etanercept once weekly for at least 1 year after secondary loss of efficacy of infliximab. The mean duration of treatment with infliximab was 32.5 ± 1.3 months. The patient cohort consisted of 3 males and 14 females, with a mean age of 56.3 ± 11.4 years and mean weight of 57.2 ± 10.9 kg. The mean duration of RA was 16.2 ± 10.9 years. The mean Disease Activity Score 28 was decreased significantly, from 5.8 at the initiation of infliximab therapy to 3.6 at the end of observation. There were no withdrawals due to adverse reactions during the study period, although in 2 subjects the agent was changed to tocilizumab due to lack of effect, one after 18 months and the other after 36 months, and 1 subject withdrew after 18 months for financial reasons. A good response can be expected to a half dose of etanercept in patients with secondary loss of efficacy of infliximab. Reduction of the patient's cost burden also makes this a superior treatment.

Keywords Cost · Etanercept · Half dose · Infliximab · Rheumatoid arthritis

Introduction

Advances in immunology and molecular biology have brought pharmacotherapy for rheumatoid arthritis (RA) closer to causal treatment [1, 2]. In 1993, Elliott et al. [3] reported dramatic results when they administered the first biologic agent, infliximab, an antibody to the cytokine tumor necrosis factor alpha (TNF-α), to patients with RA. Recently, a number of biologics have been developed [4], and they have become an essential part of pharmacotherapy for RA. They enable not only treatment of hitherto refractory cases, but also inhibition of the progression of articular destruction, with the aim of complete remission. At present, more than 1 million patients with RA worldwide are said to be on biological therapy, with corresponding costs approaching 2 trillion yen per year [5]. However, case reports have revealed several problems associated with the long-term use of biologics. These include: (1) the emergence of neutralizing antibodies, (2) complications such as infections, (3) lack or loss of efficacy, and (4) high cost [6]. Of these, high cost and secondary loss of efficacy are serious problems with biologics that require an urgent solution. In particular, the numbers of patients for whom biological therapy for RA must be discontinued for financial reasons, despite the presence of highly active disease refractory to other agents, are on the increase.

In this study, the efficacy of half-dose treatment with etanercept, at 25 mg once weekly after secondary loss of efficacy of infliximab treatment was examined.

Patients and methods

Patients

Seventeen RA patients who met the 1987 American College of Rheumatology (ACR) criteria were enrolled in this study. Assessment of secondary loss of efficacy of

H. Matsuno (✉)
Matsuno Clinic for Rheumatic Diseases, 7187-2 Kureha, Toyama, Toyama 930-0138, Japan
e-mail: info@toyama-ra.com

Table 1 Demographic and baseline characteristics of patients

Number of patients	
Male	3
Female	14
Age (years)	56.3 ± 11.4 (23–71)
Body weight (kg)	57.2 ± 10.9 (43–70)
Disease duration (years)	16.2 ± 10.2 (1–37)
Steinbrocker stage	
I	1
II	1
III	1
IV	14
Steinbrocker class	
I	1
II	6
III	10
IV	0
Duration of infliximab therapy (months)	32.5 ± 1.3 (3–60)
DAS28	5.8 ± 1.6
CRP	3.1 ± 1.9
MMP-3	251.7 ± 208.8
TSS	151.0 ± 107.2
Joint narrowing score	64.0 ± 44.9
Bone erosion score	91.4 ± 73.4

DAS28 Disease Activity Score 28, *CRP* C-reactive protein, *MMP-3* matrix metalloproteinase-3, *TSS* total Sharp score

infliximab in patients with RA was made when the Disease Activity Score 28 (DAS28) exceeded 3.2, and the treating physician determined relapse of disease based on symptoms and objective parameters. The mean duration of treatment with infliximab was 32.5 ± 1.3 months. The patients were switched from infliximab to etanercept, and continued it for at least 12 months. The mean duration of etanercept treatment was 23.6 months (range, 12–48 months). Mean patient age was 56.3 ± 11.4 years (range, 23–71 years), and mean body weight was 57.2 ± 10.9 kg (range, 43–70 kg). The mean duration of RA was 16.2 ± 10.9 years (range, 1–37 years). The numbers of patients whose disease was classified as Steinbrocker radiographic stage I, II, III, and IV were 1, 1, 1, and 14 patients, respectively. In addition, the numbers of cases classified as Steinbrocker functional class I, II, III, and IV were 1, 6, 10, and 0, respectively (Table 1).

Dosage and administration

Infliximab administration followed the standard protocol for all patients, with intravenous infusions of 3 mg/kg at 1, 2, and 6 weeks, and then every 8 weeks thereafter. The half-dose of etanercept was self-administered once weekly as a 25 mg subcutaneous injection. All patients were on combination therapy with methotrexate (MTX) at an average dosage of 7.6 mg weekly (range, 6–8 mg). As additional disease-modifying antirheumatic drugs (DMARDs) included in the combination therapy, bucillamine was administered to 13 patients and sulfasalazine to 1 patient. Various nonsteroidal anti-inflammatory drugs (NSAIDs) were taken by 15 patients, and prednisolone (PSL) was taken by 13 patients, at an average dosage of 3.8 mg/day (range, 3–8 mg/day).

Assessment

Efficacy was assessed using the European League Against Rheumatism (EULAR) response criteria and the DAS28. Before treatment was switched to etanercept, all patients received an explanation of the nature of the study and were informed that they were free to participate or withdraw from the study at any time in accordance with the Helsinki Declaration, and informed consent was obtained from them. Serum analysis, including determination of markers of disease activity such as C-reactive protein (CRP) and matrix metalloproteinase-3 (MMP-3), was performed monthly for the first 3 months and at 6-month intervals thereafter. EULAR assessments of efficacy were conducted after 12, 18, 24, and 36 months of etanercept treatment. Radiographs of both hands and both feet were obtained at the time of each assessment. Radiological findings were scored using the modified method of Van der Heijde et al. [7].

Statistical analyses were performed using Welch's *t*-test, after confirmation of group homoscedasticity.

Results

We initially registered 17 patients, and had 17 patients remaining at the 12-month assessment, with 17 patients after 18 months, 10 patients after 24 months, and 7 patients after 36 months. There were 3 withdrawals, including 2 patients (after 12 months and after 36 months) due to loss of effect; and 1 patient who changed to MTX monotherapy after 18 months, for financial reasons. There were 2 cases of adverse reactions, one of an allergic reaction at the injection site and the other of bronchitis, but both were mild with disappearance of signs and symptoms without interruption of etanercept treatment.

As shown in Fig. 1a and Table 2, the mean DAS28 scores at 0, 12, 18, 24, and 36 months after initiation of etanercept therapy were 5.8 ± 1.6, 3.5 ± 1.3, 3.7 ± 1.0, 3.7 ± 1.0, and 3.1 ± 0.9, respectively. The mean DAS28 decreased significantly from 5.8 ± 1.6 at the initiation of infliximab therapy to 3.6 ± 1.1 at the end of observation,

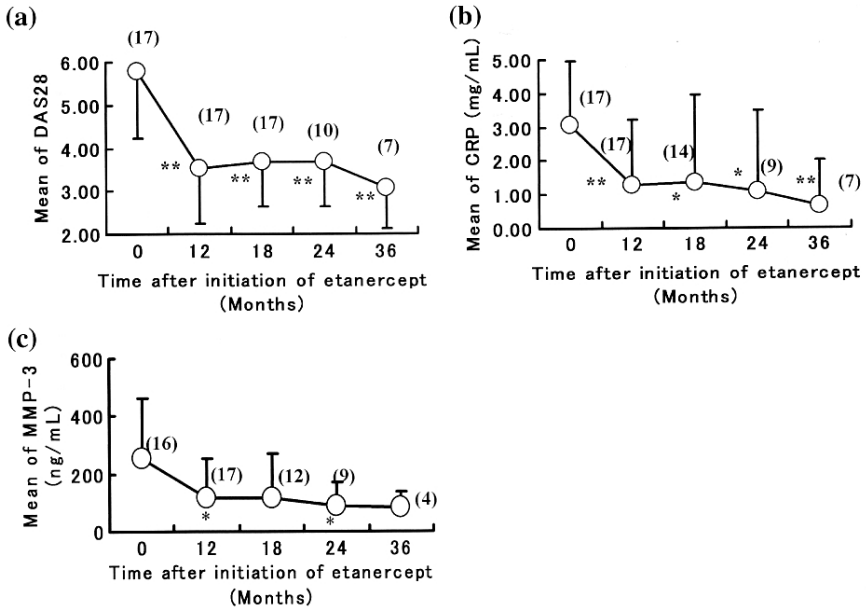

Fig. 1 Changes in **a** mean Disease Activity Score 28 (*DAS28*), **b** mean serum C-reactive protein (*CRP*) concentration, and **c** mean serum matrix metalloproteinase-3 (*MMP-3*) in patients over time (in months; *numbers in parentheses* are numbers of samples). *Circles* and *bars* indicate means and standard deviation. $*P < 0.05$, $**P < 0.01$, Welch's *t*-test compared to value at initiation of infliximab therapy (0 months after initiation of infliximab)

Table 2 Numbers of patients stratified by European League Against Rheumatism (EULAR) response criteria

Months after initiation of etanercept	12	18	24	36	At the end of observation (intention to treat; ITT)
EULAR response criteria					
Good	6	2	2	5	5
Moderate	9	13	7	2	10
No	2	2	1	0	2
Remission (DAS28 < 2.6)	3	2	1	2	3

corresponding to a moderate EULAR response. The results of the assessment for the subjects were 'good', 'moderate', and 'no response' in 5, 10, and 2 patients, respectively, with remission (DAS28 < 2.6) achieved in 3 patients. In the 2 patients with 'no response' the agent was changed to tocilizumab due to lack of effect, in one after 18 months and the other after 36 months.

Changes in the levels of CRP and MMP-3, markers of disease activity, are shown in Fig. 1b, c. The mean CRP levels at 0, 12, 18, 24, and 36 months after initiation of infliximab treatment were 3.1 ± 1.9, 1.3 ± 1.0, 1.4 ± 2.6, 1.1 ± 2.4, and 0.6 ± 1.4 mg/dL, respectively. The mean CRP level decreased significantly from 3.1 ± 1.9 mg/dL at initiation of infliximab therapy to 1.1 ± 1.2 mg/dL at the end of observation. The mean MMP-3 levels at 0, 12, 18, 24, and 36 months after initiation of infliximab treatment were 251.7 ± 208.8, 115.7 ± 138.7, 117.5 ± 154.0, 87.2 ± 82.1, and 84.5 ± 54.2 ng/mL, respectively. The mean MMP-3 level decreased significantly from 250.7 ± 208.8 at initiation of infliximab therapy to 88.5 ± 130.5 ng/mL at the end of observation.

In the 13 patients on concomitant PSL therapy, the mean daily dosage of this agent decreased significantly, from 3.8 ± 2.6 to 1.8 ± 2.7 mg/day.

Figure 2 shows individual total Sharp scores (TSS), joint space narrowing scores (JNS), and erosion scores (ES) of the 17 patients at the initiation of infliximab therapy (before) and the end of observation (after). The TSS at initiation of infliximab therapy ranged from 21 to 374. There was no patient in whom marked bone destruction was observed. The mean values of TSS were 155.4 ± 112.6 at the initiation of infliximab therapy and 151.0 ± 107.2 at the end of observation. The mean values of JNS were 64.0 ± 44.9 and 62.1 ± 42.1, and the mean values of ES were 91.4 ± 42.1 and 88.9 ± 71.3, respectively. There were no significant differences between any of these scores at the two time points.

Discussion

Since the report by Fuchs et al. [8], the treatment of RA has changed dramatically, with the introduction of DMARDs now recommended as soon as RA is diagnosed to take advantage of the "window of opportunity" before the onset of bony destruction [9]. The 2002 American College of Rheumatology *Guidelines for the management of rheumatoid arthritis* recommend commencing DMARDs,

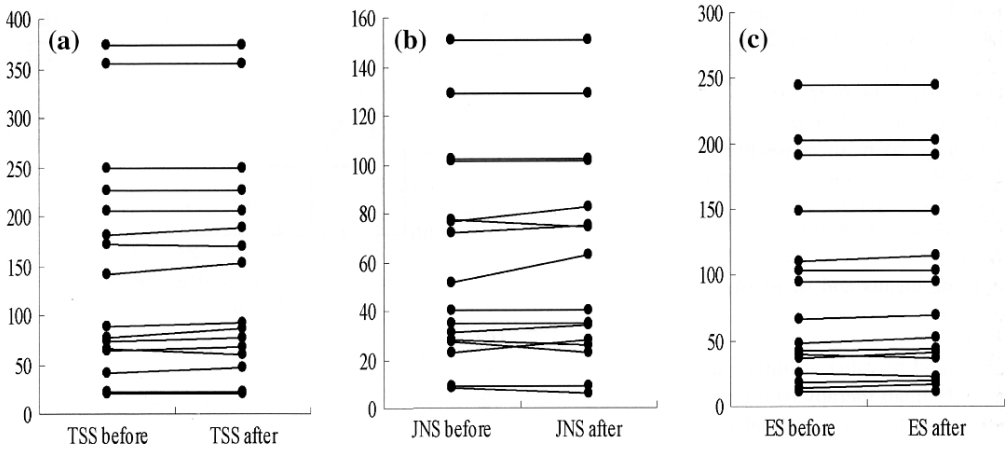

Fig. 2 Individual total Sharp scores (*TSS*) (**a**), joint space narrowing scores (*JNS*) (**b**), and erosion scores (*ES*) (**c**) of 17 patients at initiation of infliximab therapy (*before*) and the end of observation (*after*). TSS at initiation of infliximab therapy ranged from 21 to 374. There were no significant differences between any scores at the two time points

including biologics, as soon as RA is diagnosed to achieve tight disease control [10].

The TNF inhibitor infliximab has been available for use in Japan since 2003. The efficacy of infliximab and other TNF inhibitors has been confirmed by multiple studies, and these agents have become an essential part of RA treatment [3, 11–15]. One problem with the frequent use of infliximab is the emergence of human anti-chimeric antibodies (HACA), with attenuation of efficacy. In response to this, switching between TNF inhibitors has been reported since 2004, and the success rate appears to be high for switching from infliximab to etanercept [16–18]. In the present study, we were also able to achieve good results in switching from infliximab to etanercept. At half of the optimal dose, "good" or "moderate" EULAR responses were observed in 15 of the 17 patients after 1 year of etanercept administration. Furthermore, remission was achieved in 3 patients (DAS28 < 2.6).

On radiographic examination, there was no progression of bone destruction during etanercept therapy in our patients. Smolen et al. reported in their review that the TSS in patients with MTX monotherapy increased by 2.3–6.1 compared with the annual estimated progression of 10.3–25.6 in clinical studies of TNF-blocking biologics [20]. They also reported that the combination of a TNF inhibitor with MTX almost completely eliminated the progression of joint damage (score between −0.5 and 1.3). Therefore, "no progression of bone destruction" means "under control with etanercept therapy".

Although etanercept is used at the same dosage in Japan as in Western countries, we achieved favorable results with half of the optimal dose. The average weight of our patients was 57 kg, which is approximately 70–80% of the average weight of Caucasian adults, possibly accounting for the good therapeutic response to half of the optimal dose of etanercept. Halving the dosage means halving the cost borne by the patient, so this regimen can be recommended to patients who have discontinued biological therapy for financial reasons. Etanercept was approved for use in Japan for the sake of harmonization with Western countries, and the dosage and administration were correspondingly the same as those used in the West. However, in a Japanese clinical trial (TNR-001), no significant difference in efficacy was observed between groups administered etanercept at 10 mg × 2/week and 25 mg × 2/week [5]. A French study also found no difference in clinical efficacy between etanercept 25 mg once weekly and twice weekly [19]. The use of half doses of etanercept has the potential to prevent the destruction of articular cartilage. The cost of biological therapy for RA is roughly 25 times that for previous DMARDs, and at some ¥500,000 per annum corresponds to one-tenth of average annual earnings in Japan [5]. Thus, in Japan, etanercept could be commenced with half-dose treatment, considering both the relatively low body weights of Japanese patients and the costs of treatment. Future large-scale clinical trials with switching between biologic agents are needed in Japanese patients with RA to establish the appropriate dosages. This will allow better disease control, as well as reducing the costs of treatment, with favorable medical and financial effects.

Conflict of interest statement None.

References

1. Fox DA. Biological therapies: a novel approach to the treatment of autoimmune disease. Am J Med. 1995;99:82–8.
2. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996;14:397–440.
3. Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alfa. Arthritis Rheum. 1993;36:1681–90.
4. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370(9602):1861–74.
5. Matsuno H. Expensive medical expense and cost-reduction strategies in patients with rheumatoid arthritis. Clin Rheumatol Related Res. 2008;39:548–54. (in Japanese; abstract in English).
6. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of

rheumatoid arthritis: a systematic review and meta-analysis. J Rheumatol. 2006;33:2398–408.
7. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effect of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet. 1989;1:1036–8.
8. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol. 1989;16:585–91.
9. O'Dell JR. Treating rheumatoid arthritis; a window of opportunity? Arthritis Rheum. 2002;46:283–5.
10. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum. 2002; 46:328–46.
11. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Inflixamab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354(9194):1932–9.
12. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999;130:478–86.
13. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54:1063–74.
14. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicentre, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26.
15. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, et al. Efficacy and safety of the fully human anti-tumor necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003;62:1168–77.
16. Gomez-Reino JJ, Carmona L, BIOBADASER group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther. 2006;8:R29.
17. Hyrich KI, Lunt M, Watson KD, Symmons DP, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007;56:13–20.
18. Furst DE, Gaylis N, Bray V, Olech E, Yocum D, Ritter J, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. Ann Rheum Dis. 2007;66:893–9.
19. Berthelot JM, Varin S, Cormier G, Tortellier L, Guillot P, Glemarec J, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. Joint Bone Spine. 2007;74:144–7.
20. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370:1861–74.