Effects of half dose etanercept (25 mg once a week) on clinical remission and radiographic progression in patients with rheumatoid arthritis in clinical remission achieved with standard dose

B. Raffeiner, C. Botsios, F. Ometto, L. Bernardi, R. Stramare, S. Todesco, P. Sfriso, L. Punzi

Abstract

Objective

This prospective long-term follow-up study evaluated the effects of half-dose etanercept (25 mg weekly) on clinical remission and radiographic progression in a large cohort of patients with rheumatoid arthritis (RA) in clinical remission after etanercept 25 mg bi-weekly.

Methods

524 biologic-naïve RA patients were treated with etanercept 25 mg bi-weekly after failure of conventional drugs. Patients achieving remission (DAS28 <2.6) for ≥12 months were randomised to receive etanercept 25 mg weekly or 25 mg bi-weekly. Patients were assessed at baseline and every 12 weeks. Remission rates, radiographic progression, incidence of infections and costs of the regimens were compared.

Results

After a mean follow-up of 18±11 months, 347 patients (66.2%) achieved DAS28 remission; 323 were randomised to one of two dose regimens: etanercept 25 weekly (group A, 159 patients) and etanercept 25 mg bi-weekly (group B, 164 patients). At the end of follow-up, 81.8% patients of group A maintained remission for a mean of 3.6±1.5 years. Radiographic progression occurred in a small number of patients of group A and the rate of radiographic progression (TSS >0) was not significantly different in the two groups (18.85% vs. 19.0% after the first year and 16.9% vs. 21.6% after the second year, respectively). The incidence ratio of severe infections was 2.3/1.000 patient-years in group A. Etanercept half-dose regimen resulted in a saving of €3.190.545 with a cost saving up to €827.318 per year.

Conclusion

Clinical remission and arrest of radiographic progression persisted in a substantial percentage of patients with RA even after reduction of standard-dose etanercept.

Keywords

rheumatoid arthritis, disease activity score, remission, radiographic progression, etanercept, low dose
Half dose etanercept in rheumatoid arthritis / B. Raffeiner et al.

Berrad Raffeiner, MD, PhD
Costantino Botsios, MD, PhD
Francesca Ometto, MD
Livio Bernardi, MD
Roberto Stramare, MD, PhD
Silvano Todesco, MD
Paolo Sfriso, MD, PhD
Leonardo Punzi, MD, PhD

Please address correspondence to:
Costantino Botsios, MD, PhD,
via Giustiniani 2, 35128 Padova, Italy.
E-mail: constantin.botsios@unipd.it

Received on May 3, 2014; accepted in revised form on July 29, 2014.
© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2015.

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by erosive polyarthritis that leads to joint destruction, disability and handicap. As a consequence, the majority of patients with RA incur work loss, quality of life impairment and premature death (1). The tumour necrosis factor (TNF) inhibitor etanercept (ETA) is approved for the treatment of patients with moderate to severe active RA. Randomised clinical trials have shown that it improves the signs and symptoms of early and long-standing RA, prevents radiographic progression and ameliorates health-related quality of life (2–4). However, although it is accepted that ETA is cost-effective compared with traditional disease-modifying anti-rheumatic drugs (DMARDs), treatment costs with TNF inhibitors at recommended doses are high, and there remains some concerns over an increased risk of infections with long-term therapy with TNF inhibitors, including standard dose ETA (4, 5). Therefore, in our study we evaluated the effects of half dose ETA (25 mg/weekly) on clinical remission and radiographic progression in patients with RA in clinical remission previously achieved with standard dose (25 mg bi-weekly). Secondary endpoints were to evaluate the frequency of adverse events and cost savings after halving the ETA dose.

Methods
Study design and patients
This prospective long-term follow-up study was conducted in a single Italian academic center (Rheumatology unit, Department of Medicine, University of Padova). Between January 2006 and December 2012 a cohort of 524 biologic-naïve patients with RA as defined by 1987 ACR criteria (6) were treated with ETA 25 mg bi-weekly after the failure of traditional synthetic DMARDs and evaluated every three months for disease activity. Among this cohort, patients who achieved a disease activity score (7) using a 28-joint assessment based on erythrocyte sedimentation rate (DAS28-ESR) <2.6 for at least 12 months were randomised to one of the following two subcutaneous dose regimens: ETA 25 mg weekly (group A) or ETA 25 mg bi-weekly (group B). The randomisation was done in a consecutive manner, 1:1, and treatment was continued until disease flare-up.

Patients received ETA 25 mg in prefilled syringes for subcutaneous injection. Qualified personnel instructed all patients in correct injection technique and directly observed self-administration of the first dose. The drug was delivered bi-monthly to each patient in a package containing four prefilled syringes, and all patients were instructed on how to store the drug protected from light at 2–6°C. They were not permitted variations to the dosage of steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and DMARDs during the study period. Intra-articular steroids were not permitted during the study period. In the event of pain, the patients were allowed to take analgesics (acetaminophen or tramadol).

The local ethics committee reviewed and approved the study protocol. Before entering the study, each patient was informed of the nature, duration, and purpose of the study, as well as all the potential benefits and drawbacks that could be expected. All participants gave their written informed consent. The study was conducted in compliance with the Declaration of Helsinki of 1975/83.

Clinical evaluations
Patients were followed by the same rheumatologist, and follow-up visits were scheduled at baseline and every 3 months thereafter. The patients were evaluated for remission as the primary outcome measure at enrolment and at every follow-up visit. Intervals between control visits were shortened in the event of urgent clinical problems. At every visit, patients had a complete physical examination. Disease activity was assessed using the DAS-ESR on 28 joints (7). Disease flare-up was defined as presentation of a DAS28 value >2.6 at any follow-up visit. Routine blood examinations, including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anticyclic citrullinated proteins antibodies (anti-CCP), complete blood cell count with differential count, renal and liver function tests, and antinuclear antibod-
ies were also carried out. All patients were monitored for clinical and laboratory evidence of adverse events. Infections were considered as severe when parenteral antibiotics and/or hospitalisation were required. The date of the last visit constituted the end of follow-up, which was extended to December 2012.

Joint damage was evaluated on hand and feet x-rays performed at baseline, and then after one and after two years. A radiologist, experienced in musculoskeletal pathologies and blinded to the clinicians and the treatments of the patient, calculated according to the van der Heijde’s modified total Sharp score (TSS) in the 2 groups (8), performed after one and after two years.

Progression was reported as absolute radiographic progression (ΔTSS > 0) and as real progression (ΔTSS ≥ 5) according to the smallest detectable difference defined for this scoring system (8). Structural progression rates were compared between the 2 groups. Yearly progression of structural damage prior to biologic treatment was calculated for each patient with the radiographs preceding the biologic therapy and was expressed as ATSS/year.

The incidence ratio with 95% confidence intervals of total and severe infections per 1,000 patient-years was calculated by Mid-P exact test modified by Miettinen with software OpenEpi Version 2 in the half dose and in the standard dose ETA group (9). Cost savings deriving from half dose ETA were calculated according to national Italian pharmacy prices, including taxes, using data sourced from the Italian pharmacy schedule (http://www.uvef.it/ecm/web/uvef/home/farmaci/schede-hta-farmaci). Annual and total cost savings per patient were calculated from the time of the introduction of half dose therapy. Indirect costs were not included in the analysis.

Statistical analysis
Remission retention rates on half dose and on all ETA therapies were determined with Kaplan-Meier survival curves and compared by log rank test.

All data were analysed using statistical software (SPSS Inc., Chicago, Illinois, USA, version nr. 18). All comparisons were controlled for statistical significance by Mann-Whitney U-test or exact Fisher test as appropriate. Statistical significance was considered when p < 0.05.

Results
Patient demographics and baseline characteristics
From January 2006 to December 2012, 524 patients with RA (421 females and 103 males; mean age 48.3±20.2 years; mean disease duration 11.5±8.7 years; mean DAS28 6.2±1.2) were treated with ETA 25 mg bi-weekly. After a mean follow-up of 18±11 months, 347 (66.2%) of patients were in DAS28 remission. Of these patients, 323 agreed to participate in the study and were randomised to receive ETA 25 mg weekly (group A) and 25 mg bi-weekly (group B).

Table I shows demographics, clinical, and radiographic characteristics of the two groups at baseline. No differences were found between the two groups of patients regarding positivity of autoantibodies, extra-articular manifestations, concomitant therapy with steroids, NSAIDs and DMARDs, comorbidities and ATSS/year. In group A and B (323 patients), higher disease activity prior biologic therapy was associated with higher radiographic damage at baseline (ΔTSS/year 12.3±8.8 vs. 8.7±5.7; p = 0.008), and was treated more frequently with concomitant DMARDs (76.7% vs. 61.0%; p = 0.004).

Maintenance of remission on half dose etanercept
At the end of the observational period, 130 patients out of 159 (81.8%) maintained remission with ETA 25 mg weekly for a mean of 3.6±1.5 years, as estimated by the Kaplan-Meier survival curve (Fig. 1). These 130 patients were slightly younger than those who failed dose reduction (55.2±14 vs. 61±8.9 years; p = 0.04) and were taking fewer NSAIDs (17.6% vs. 39.3%; p = 0.02).

Disease activity prior to biologic therapy did not influence response to ETA half dose. Failure to maintain remission with ETA half dose occurred in 29 patients (18.2%). All these patients returned to standard dose after remission was recognised to be lost: 62.1% during the first year, 27.6% during the second year and 10.3% during the third year on ETA half dose. Most of the patients failing dose reduction regained remission with standard dose, except 7 (24.1%), who were switched to other biologic agents.

Prevention of progression
Half dose ETA was very effective in preventing radiographic progression. Radiographic progression occurred only in a minority of patients treated with ETA half dose (Fig. 2), and the rate was not different from that of patients

<table>
<thead>
<tr>
<th>Table I. Baseline characteristics of the study patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>n=159</td>
</tr>
<tr>
<td>Mean age, years ±SD</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Mean disease duration, years ±SD</td>
</tr>
<tr>
<td>Mean DAS28 prior to etanercept therapy ±SD</td>
</tr>
<tr>
<td>Rheumatoid factor or anti-CCP positive patients, n (%)</td>
</tr>
<tr>
<td>Mean TSS at baseline ±SD</td>
</tr>
<tr>
<td>Mean ATSS/year prior to etanercept ±SD</td>
</tr>
<tr>
<td>Mean concomitant prednisone, mg/day ±SD</td>
</tr>
<tr>
<td>Patients on concomitant NSAIDs, n (%)</td>
</tr>
<tr>
<td>Patients on concomitant DMARDs, n (%)</td>
</tr>
<tr>
<td>n. of previous DMARDs prior to etanercept therapy, mean±SD</td>
</tr>
<tr>
<td>n. of comorbidities, mean±SD</td>
</tr>
</tbody>
</table>

*Group A, half dose, Group B, standard dose etanercept; * methotrexate or leflunomide.
DAS: disease activity score; anti-CCP: anti-cyclic citrullinated proteins; DMARDs: disease-modifying anti-rheumatic drugs; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation; TSS: total Sharp score.
on standard dose. This observation was true both in the first and in the second year of observation \((p=\text{n.s.})\). After the first year the rate of patients who had experienced \(\Delta\text{TSS} \geq 0\) or \(\Delta\text{TSS} \geq 5\) was 17.6\% and 1.25\%, respectively, on half dose \textit{versus} 17.8\% and 1.2\% on standard dose. After 2 years it was 15.5\% and 1.4\% on half dose \textit{versus} 20.0\% and 1.6\% on standard dose. No difference in radiographic progression was seen between severe and moderate disease activity prior to ETA treatment in either the half or standard dose group, even in the patients who failed dose reduction (Fig. 3).

**Risk of infections**

Group A patients had significantly fewer total infections than patients in group B (104 vs. 172 infections per 1,000 patient-years; \(p<0.001\)). The incidence ratio of severe infections was 2.3 per 1,000 patient-years in group A and 6.7 in group B, although this difference was not statistically significant.

**Therapy discontinuation**

A total of 15 patients of group A (9.4\%) discontinued ETA therapy until the end of study: 7 (4.4\%) patients due to inefficacy, 6 (3.8\%) due to adverse events, 1 patient wanted to become pregnant, and 1 patient was lost to follow-up. The overall drop-out rate from ETA therapy during the study period (mean 3.4±1.6 years) was not significantly different between half dose and standard dose patients (Fig. 4).

**Treatment costs**

Analysis of treatment costs of the biologic therapy showed that successful ETA dose reduction saved \(\text{€3.190.545.13}\) since its introduction. This treatment strategy continues to produce a cost saving of \(\text{€827.318.71}\) every year.

**Discussion**

Our data demonstrate that half dose ETA is very effective in maintaining clinical remission induced by standard dose ETA in a large proportion of patients with established RA (81.8\%), and all patients maintained their remission through a mean follow-up of 3.6±1.5 years.

Two considerations are pivotal to clarify the efficacy of lower dosages: first, in remission, circulating TNF-\(\alpha\) levels are expected to be not as high as in active disease; then, the favourable neutralising profile of ETA makes lower doses sufficient to keep patients in remission.

ETA has unique pharmacokinetics and pharmacodynamics, that are different from the other TNF-\(\alpha\) inhibitors, and that could make it suitable for dose adjustments. Moreover, the maximum serum concentrations and the area under the serum concentration-time curve of weekly ETA 25 mg are similar to those of weekly ETA 50 mg (10).

Recent data showed differences among the TNF-\(\alpha\) inhibitors in the neutralisation potency of soluble TNF-\(\alpha\) (sTNF-\(\alpha\)) being dependent on the concentration of TNF-\(\alpha\) in the serum. At high concentrations of sTNF-\(\alpha\) (>2 ng/mL), as found in inflamed tissues, all TNF-\(\alpha\) inhibitors neutralise sTNF-\(\alpha\) with similar potency. Whereas, at low concentrations of sTNF-\(\alpha\) (<0.1 ng/mL), as expected in the case of disease remission, ETA neutralises sTNF-\(\alpha\) with more than 20-fold higher potency than the other TNF-\(\alpha\) inhibitors (11).

Thus, ETA appears particularly suitable for dose reduction once patients have gained remission.
Moreover, our data show that half dose ETA halts radiographic damage as effectively as standard dose. The majority of patients (about 80%) reached radiographic remission, while 20% showed minor radiographic changes and just 1.5% of patients experienced a relevant progression among all groups, with no differences as far as disease activity, past radiographic progression, concomitant medications or ETA dose was concerned. Effects were also sustained in the second year of treatment.

Notably, patients who flared during dose reduction, and thus returned to full dose, did not show a greater radiographic progression. That being so, low dose ETA seems to prevent radiographic damage even if full clinical response is not achieved. There, in fact, some discordancy between the clinical and the structural effects. It has been reported that therapy with TNF antagonists (infliximab, ETA) in RA modulates the OPG/RANKL system, a potential mechanism that could explain the retardation of radiographic damage (12, 13).

A second concern relates to secondary failure of ETA therapy caused by the reduction of dosage. Eventual failure of TNF-α inhibitor therapy is a crucial point in the treatment of RA patients and leads to either dose increase or to a switch to other biologics (14, 15). Our experience in this matter is reassuring, as the majority of patients failing half dose ETA regained remission with full dose therapy. The need to switch to other biologic agents was rare and it occurred with similar frequency in the low and in the standard dose group. Accordingly, it could be assumed that patients failing both half dose and re-adjustment to full dose would have probably lost disease control anyway.

With regard to side effects, in the half dose ETA group significant less total infections compared to full dose group and a trend for fewer severe infections were observed. TNF-α inhibitors are demonstrated to be safe, but increased rates of infections is sometimes related to higher doses (16). Although a direct relationship between infectious risk and TNF-α dose has not definitively been established, half dose ETA appears to be particularly safe and could be of advantage in elderly patients on TNF-α therapy presenting disease related or unrelated comorbidities making them prone to infections.

In a recent randomised controlled trial (17), patients with moderately active RA (DAS28 >3.2 and ≤5.1) despite treatment with methotrexate (15–25 mg weekly) received 50 mg ETA plus methotrexate every week. Patients who achieved sustained low disease activity were randomly assigned to one of three treatment groups: 50 mg ETA plus methotrexate, 25 mg ETA plus methotrexate, or placebo plus methotrexate. The results in this study are comparable with our data. In fact, reduced doses of ETA effectively maintained low disease activity.

Finally, adopting a low dose ETA strategy leads to the gain of considerable

---

**Fig. 3.** Radiographic progression in patients on half dose etanercept (Group A) and patients on standard dose etanercept (Group B) according to moderate and high disease activity prior to etanercept treatment, and in patients failing DAS28 remission on half dose etanercept (p=NS) ∆TSS = 0: no progression, ∆TSS >0: absolute progression, and ∆TSS ≥5: real progression. TSS: total Sharp score.

**Fig. 4.** Kaplan-Meier curves of the drop-outs from etanercept therapy in patients on half dose etanercept (Group A) and patients on standard dose etanercept (Group B) during the study period.
cost savings, particularly in established RA, when therapy discontinuation is demanding, but it may be applied to earlier disease too. A recent study combined clinical trial and daily practice data to explore different treatment scenarios in early RA. The results indicate that, in a situation where a considerable proportion of patients achieve remission, dose-adjustments will increase the cost-effectiveness of ETA treatment (18). Strategies of drug discontinuation and dose reduction may become essential part of the “treat-to-target” approach (19, 20).

The resources so gained could be invested for candidate patients for TNF-α inhibitor or other biologic therapy, especially in situations where policy maker intervention sets limitations to contain ever more increasing health care costs. Considering our calculated annual cost of €6,315.41 per patient for Italy, low dose ETA is the lowest priced biologic treatment protocol available that meets the present standards in RA therapy, that is, clinical and radiographic remission, safety and cost-effectiveness.

Conclusion

Our study suggests that clinical remission and arrest of radiographic progression remain in a high percentage of patients with RA even after reduction of full dose ETA. This finding has important economic implications. Furthermore, maintenance of remission with low dose ETA leads to new strategies in the long-term management of RA patients.

References