CONCISE REPORT

Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients

A Jamnitski,1 C L Krieckaert,1 M T Nurmohamed,1,3 M H Hart,2 B A Dijkmans,1,3 L Aarden,2 A E Voskuyl,3 G J Wolbink1,2

ABSTRACT

Objective To investigate the relationship between serum etanercept levels and clinical response.
Methods In 292 etanercept-treated patients with rheumatoid arthritis clinical and pharmacological data were determined at baseline and after 1, 4 and 6 months of etanercept treatment. Differences in etanercept levels between good, moderate and European League Against Rheumatism (EULAR) non-responders were assessed after 6 months of therapy.
Results After 6 months of therapy etanercept levels were significantly higher in good responders (median (IQR) 3.78 (2.53–5.17)) compared with both moderate 3.10 (2.12–4.47) and EULAR non-responders 2.80 (1.27–3.93) (all p<0.05). There was a significant association between clinical response and serum etanercept levels (regression coefficient 0.54, 95% CI 0.21 to 0.86, p=0.001). When patients were categorised into quartiles according to the height of etanercept levels, the lowest quartile (etanercept level <2.1 mg/l) comprised 40% of all non-responders. The highest quartile (etanercept level >4.7 mg/l) comprised 35% of all good EULAR responders. Anti-etanercept antibodies were detected in none of the sera.
Conclusion The authors demonstrated that lower etanercept levels were associated with non-response. Therapeutic drug monitoring and the possibility of the adjusted dosing regimes in the selected groups of patients should be investigated further as a possible tool to optimise treatment with etanercept.

Although the efficacy of etanercept 50 mg per week has been demonstrated, a low number of patients achieve clinical remission.1 Furthermore, the administration of higher etanercept doses did not lead to additional efficacy in patients with suboptimal response to the standard dose of 50 mg per week.2 Until now, decision making in the case of failure to anti-tumour necrosis factor (TNF) treatment was based on clinical outcome alone, without taking into account circulating drug levels.3 However, pharmacological and disease-related aspects may both influence drug efficacy.4 For example, a low synovial expression of TNFα has been associated with lack of response to anti-TNF treatment.5

Previously, an association between low circulating drug levels and lack of clinical response was demonstrated for infliximab and adalimumab-treated patients.6 7 In contrast, no association was found between etanercept drug levels and clinical response.2 8 Furthermore, antibodies against etanercept, all non-neutralising, were measured in less than 2% of the patients.8–10 In rheumatoid arthritis (RA) patients, a lower response to etanercept was associated with high levels of disability, the presence of IgM rheumatoid factor and etanercept monotherapy.11 12

Although a personalised treatment strategy has been proposed for patients treated with TNF inhibitors,6 16 the clinical consequence of monitoring circulating etanercept levels is not yet clear. Therefore, we aimed to investigate the association between circulating etanercept levels and clinical response in a large cohort of etanercept-treated RA patients.

PATIENTS AND METHODS

Study population
The study population consisted of patients with RA, all treated with etanercept, included in an observational cohort. Inclusion criteria for this cohort were RA according to the American College of Rheumatology 1987 criteria,13 age 18 years or older, failure on at least two disease-modifying antirheumatic drugs including methotrexate14 and active disease as measured by the disease activity score in 28 joints (DAS28) >5.1. Patients were treated with either concomitant medication, including methotrexate and prednisone, or etanercept monotherapy. All patients used etanercept 50 mg subcutaneously every week or 25 mg twice a week. None of the patients received a dose increase of etanercept during the 6 months of the observation period. The study was approved by the local medical ethics committee and all patients gave written informed consent.

Clinical response to etanercept
Disease activity was assessed at baseline and after 1, 4 and 6 months of therapy by the DAS28 joints. Clinical response was assessed using the European League Against Rheumatism (EULAR) response criteria.15

Measurement of serum etanercept levels and antietanercept antibodies
Serum etanercept levels were measured by ELISA based on the ability of etanercept to bind TNF. Antibodies against etanercept were measured by two-site radio immune assay, bridging ELISA and
Clinical and epidemiological research

Table 1  Demographic and clinical characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=292)</th>
<th>Good responders† (n=103)</th>
<th>Moderate responders† (n=115)</th>
<th>Non-responders† (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>52.8±12.7</td>
<td>50.5±11.7†</td>
<td>54.4±12.7†</td>
<td>53.7±13.8</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>239 (82)</td>
<td>79 (77)</td>
<td>95 (83)</td>
<td>65 (88)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.0±5.6</td>
<td>25.9±5.4</td>
<td>25.7±5.2</td>
<td>26.7±6.5</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>77 (27)</td>
<td>32 (32)</td>
<td>29 (26)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Glomerular filtration rate§</td>
<td>118±39.3</td>
<td>121.5±38.1</td>
<td>114.8±39.8</td>
<td>120.6±40.7</td>
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<tr>
<td>DMARD and previous biological therapy</td>
<td></td>
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<tr>
<td>Previous DMARD</td>
<td>2.9±1.2</td>
<td>2.7±1.1†</td>
<td>3.0±1.4†</td>
<td>3.0±1.3*</td>
</tr>
<tr>
<td>Methotrexate use, n (%)</td>
<td>223 (76)</td>
<td>82 (80)</td>
<td>87 (76)</td>
<td>54 (73)</td>
</tr>
<tr>
<td>Methotrexate dose, mg/week</td>
<td>19.7±7.0</td>
<td>20.9±6.3</td>
<td>19.3±7.5</td>
<td>18.8±7.2</td>
</tr>
<tr>
<td>Prednisone use, n (%)</td>
<td>83 (28)</td>
<td>26 (25)</td>
<td>35 (30)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>Prednisone dose, mg/day</td>
<td>8.2±3.9</td>
<td>7.3±4.1</td>
<td>8.5±3.9</td>
<td>8.6±3.7</td>
</tr>
<tr>
<td>Other DMARD than methotrexate, n (%)</td>
<td>96 (33)</td>
<td>41 (40)</td>
<td>34 (30)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Previous biological agent, n (%)¶</td>
<td>89 (31)</td>
<td>19 (18)**</td>
<td>41 (36)†</td>
<td>29 (39)*</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disease duration, years</td>
<td>8 (3–16)</td>
<td>8 (2–4)††</td>
<td>9 (3–8)‡</td>
<td>7 (3–7)</td>
</tr>
<tr>
<td>Rheumatoid factor, n (%)</td>
<td>207 (72)</td>
<td>74 (73)</td>
<td>84 (74)</td>
<td>49 (66)</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
<td>206 (72)</td>
<td>70 (69)</td>
<td>83 (74)</td>
<td>53 (72)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.3±0.7</td>
<td>1.2±0.8</td>
<td>1.4±0.7</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.2±1.3</td>
<td>5.0±1.2†</td>
<td>5.7±1.2**</td>
<td>4.7±1.5***</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>23 (12–30)</td>
<td>17 (9–31)††</td>
<td>29 (14–46)***</td>
<td>20 (10–40)***</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>8 (3–1)</td>
<td>6 (3–20)</td>
<td>11 (4–23)**</td>
<td>6 (2–17)**</td>
</tr>
</tbody>
</table>

Mean values±SD, median and IQR, or percentages are shown.
†There was a significant difference between EULAR good and non-responders for previous DMARD (p=0.047) and previous biological agent use (p=0.002).
‡Last observation carried forward data were used for patients who discontinued the treatment with etanercept before 6 months.
¶There was a significant difference between good and moderate EULAR responders for age (p=0.017); previous DMARD (p=0.0034); DAS28 (p<0.001); previous biological agent use (p=0.005); disease duration (p=0.038) and erythrocyte sedimentation rate (p=0.001).
∗Glomerular filtration rate according to the Cockcroft–Gault formula.
†Previous biological agents consisted of infliximab and adalimumab.
**There was a significant difference between moderate and EULAR non-responders for DAS28 (p<0.001); erythrocyte sedimentation rate (p=0.039); C-reactive protein (p=0.033).
DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire.

IgG4-ABT. The details on these assays are added as supplementary text, available online only.

Statistical analysis

Data are shown as mean (SD), median (IQR) or percentages. Differences between good, moderate and non-responders were evaluated by using an independent t test, χ² or Mann–Whitney test, if appropriate. Analyses were performed using the method of last observation carried forward for patients who discontinued the treatment with etanercept before 6 months. To investigate whether etanercept levels were influenced by confounders multiple regression analyses were performed. All baseline variables were considered as potential confounders and included in the model if the β changed 10% or more. Logistic regression analyses were performed to examine the association between height of the serum etanercept levels and EULAR response. p Values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics and clinical response

Clinical and demographic characteristics of all patients are shown in table 1. Eighty per cent of the patients (234/292) completed 6 months of etanercept treatment. Of the 58 patients who discontinued etanercept treatment before 6 months, 35 patients stopped due to inefficacy, 15 because of adverse events and eight patients stopped for reasons such as relocation, unwillingness to participate and lost to follow-up.

After 6 months of etanercept treatment, 103 (36%) patients were good, 115 (39%) were moderate and 74 (25%) were non-responders according to the EULAR response criteria (table 1).

Changes in serum etanercept levels

At baseline, serum etanercept levels were undetectable. Median (IQR) etanercept levels in all patients were 3.17 mg/l (1.90–4.53), 3.25 mg/l (2.06–4.71) and 3.44 mg/l (2.34–4.78) after 1, 4 and 6 months of etanercept treatment, respectively.

When stratified for EULAR response serum etanercept levels were significantly higher in good responders compared with both moderate and EULAR non-responders at all time points (all p<0.05). There were no statistical differences in etanercept levels between moderate and EULAR non-responders: p=0.93, p=0.09 and p=0.05 at 1, 4 and 6 months, respectively (table 2).

A sensitivity analysis was performed for patients who completed 6 months of etanercept treatment; this did not alter the results (data not shown).

In univariate linear regression, an association between etanercept levels and EULAR response was found (regression coefficient 0.54, 95% CI 0.21 to 0.86, p=0.001) (see also supplementary table 1S, available online only). Confounding analyses were performed by multiple regression analysis. All baseline characteristics were used as potential confounders, no confounders were found.

In addition, we stratified all patients into quartiles according to the height of the etanercept level (figure 1). When patients in...
the highest quartile were compared with patients in the lowest quartile, patients in the lowest quartile were predominantly women (89% vs 68%, p=0.002), used lower doses of methotrexate (12.6±9.9 vs 16.9±10.1, p=0.01), had a higher body mass index (BMI) (27.5±6.3 vs 24.9±4.3, p=0.007), and had a higher glomerular filtration rate (130.0±46.6 vs 107.8±29.4, p=0.001). Logistic regression analyses demonstrated a significant association between the height of serum etanercept levels and EULAR response (OR 2.5, 95% CI 1.58 to 3.98, p<0.001). Correction for the potential confounding variable glomerular filtration rate did not change the results (OR 2.91, 95% CI 1.71 to 4.95, p<0.001).

The percentage of EULAR good responders was significantly different between the highest and the lowest quartiles (p<0.001). The same was true for EULAR non-responders (p=0.001) (figure 1).

Anti-etanercept antibodies were not detected in any of the sera.

**DISCUSSION**

This study demonstrates for the first time a clear correlation between the height of the serum etanercept level and clinical response. Patients with RA who did not respond to etanercept treatment achieved lower etanercept levels compared with responding patients. We observed that 40% of all non-responding patients had an etanercept level below 2.1 mg/l, which is considerably lower than the average concentration of 3 mg/l found in pharmacokinetic studies. However, as the dose increase in patients with suboptimal response based on clinical data alone was not effective, our data suggest that it might be useful to assess the effect of dose increase only in non-responding patients with the lowest etanercept levels (<2.1 mg/l). This personalised treatment approach could be effective and needs to be investigated further. Moreover, we demonstrated that 35% of all responding patients had an etanercept level above 4.7 mg/l; in these patients etanercept dose reduction or interval extension might be possible without the loss of clinical response.

The elimination routes of etanercept are not well documented. An immune response against a drug is a probable cause of accelerated drug clearance. In the current study, we attempted to measure (neutralising) antibodies against etanercept and did not detect them. An explanation for the absence of anti-etanercept antibodies could be a less immunogenic structure of etanercept as only the fusion part of the molecule may contain neoepitope regions to which an immune response can be directed, this is not the functional part of the molecule. Furthermore, drug interference may lead to an underestimation of anti-etanercept production, as antibody detection is only possible if anti-etanercept production exceeds the concentration of the drug present in the serum.

In this study, patients with low etanercept levels had a significantly higher BMI and were predominantly women. These findings are consistent with other studies reporting that the pharmacokinetics of etanercept can be assessed in patients with high disease activity and all responding patients detected in this study underline the importance of therapeutic drug monitoring including measurement of the serum drug levels combined with clinical parameter assessment. We suggest that adjusted dosing regimes might be needed in a selected group of patients and it might be more cost-effective to adjust etanercept dosages according to serum etanercept concentrations, taking into account the high cost of etanercept. More studies are needed to provide evidence for this approach.

**Table 2** Etanercept levels in good, moderate and non-responders

<table>
<thead>
<tr>
<th></th>
<th>Good responders</th>
<th>Moderate responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month</td>
<td>3.40 (2.22–4.62)†</td>
<td>2.52 (1.26–4.11)†</td>
<td>2.64 (1.20–3.89)*</td>
</tr>
<tr>
<td>4 Months</td>
<td>3.98 (2.72–5.35)†</td>
<td>3.08 (2.03–4.52)†</td>
<td>2.54 (1.12–3.94)*</td>
</tr>
<tr>
<td>6 Months</td>
<td>3.78 (2.53–5.17)†</td>
<td>3.10 (2.12–4.47)†</td>
<td>2.80 (1.27–3.93)†</td>
</tr>
</tbody>
</table>

Etanercept levels are shown in mg/l.

*There was a significant difference between good and European League Against Rheumatism (EULAR) non-responders p=0.009 at 1 month and p<0.001 at 4 and 6 months after the start of etanercept treatment.
†There was a significant difference between good and moderate EULAR responders p=0.004 at 1 month, p=0.001 at 4 months and p=0.045 at 6 months after the start of etanercept treatment.

In summary, the differences in etanercept levels between responding and non-responding patients detected in this study underline the importance of therapeutic drug monitoring including measurement of the serum drug levels combined with clinical parameter assessment. We suggest that adjusted dosing regimes might be needed in a selected group of patients and it might be more cost-effective to adjust etanercept dosages according to serum etanercept concentrations, taking into account the high cost of etanercept. More studies are needed to provide evidence for this approach.

**Contributors** All authors were involved in drafting the paper or revising it critically for important intellectual content, and all authors approved the final version to be published. All had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Competing interests** MTN has received consultancy fees from Abbott, Roche, Pfizer, MSD, UCB, BMS and Wyeth, payment for lectures from Abbott, Roche and Pfizer and research grants from Abbott, Roche and Pfizer. BAD has received research...
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Patient consent obtained.

Ethics approval The study was approved by the medical ethics committee of Reade and Slotervaart Ziekenhuis.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


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