The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept

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Ann Rheum Dis published online November 10, 2010
doi: 10.1136/ard.2010.135111

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The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept

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ABSTRACT

Objective The aim of this study was to test the hypothesis that the reason for non-response (caused by immunogenicity or not) to a first tumour necrosis factor (TNF) inhibitor defines whether a second TNF inhibitor will be effective.

Methods This cohort study consisted of 292 consecutive patients with rheumatoid arthritis (RA), all treated with etanercept. A total of 89 patients (30%) were treated previously with infliximab or adalimumab (‘switchers’), and the remaining 203 (70%) were anti-TNF naive. All switchers were divided into two groups: with and without antibodies against the previous biological. Differences in clinical response to etanercept between switchers with and without antibodies and patients who were anti-TNF naïve were assessed after 28 weeks of treatment using changes in Disease Activity Score in 28 joints (DAS28).

Results After 28 weeks of treatment, response to etanercept did not differ between patients who were anti-TNF naïve and switchers with anti-drug antibodies (ΔDAS28 = 2.1 ± 1.3 vs ΔDAS28 = 2.0 ± 1.3; p = 0.743). In contrast, switchers without anti-drug antibodies had a diminished response to etanercept treatment compared to patients who were TNF naïve (ΔDAS28 = 1.2 ± 1.3 vs ΔDAS28 = 2.1 ± 1.3; p = 0.001) and switchers with antibodies (ΔDAS28 = 1.2 ± 1.3 vs ΔDAS28 = 2.0 ± 1.3; p = 0.017).

Conclusion Patients with RA with an immunogenic response against a first TNF-blocking agent had a better clinical response to a subsequent TNF blocker compared to patients with RA without anti-drug antibodies. Hence, determining immunogenicity can be helpful in deciding in which patient switching could be beneficial and can be part of a personalised treatment regimen.

INTRODUCTION

Tumour necrosis factor (TNF) is a proinflammatory cytokine that plays a pivotal role in chronic inflammatory diseases such as rheumatoid arthritis (RA), Crohn’s disease and ankylosing spondylitis. Biologicals directed against TNF have revolutionised treatment for RA. Currently, infliximab, adalimumab and etanercept are widely used for the treatment of RA.1 They are biologically active molecules, varying from chimaeric to humanised and ‘fully human’, and can incite immune reactions in humans.2 Anti-drug antibody formation has been associated with non-response to therapeutic monoclonal antibodies (TmAbs) for the treatment of RA (infliximab and adalimumab) and Crohn’s disease (infliximab).3–5 The anti-drug immune response can lead to immune complex formation (therapeutic drug antibody with anti-drug antibody) that can promote the rapid clearance of the drug resulting in low trough levels.6

Several therapeutic strategies are available for a patient not responding to a first TNF inhibitor, that is, switching to another TNF inhibitor, switching to a biological with another mechanism of action (eg, rituximab or abatacept) or a change in dosage regime of the current TNF inhibitor. Since more biological agents are available for the treatment of RA, switching from one TNF inhibitor to another in case of failure or adverse events has become a common approach in daily clinical practice.7 However, the usual rationale for switching to another TNF inhibitor in daily practice is currently based on clinical data, instead of based on understanding what mechanism caused non-response in an individual patient and how that will influence the patient’s future treatment response. Previous studies have shown that switching between TNF inhibitors can be beneficial.8,9 In general, treatment response observed in switchers was lower than in patients who were anti-TNF naïve.7,10,11 Results after switching were better in patients who stopped their first-course TNF inhibitor due to adverse events rather than inefficacy.12–14

Recently, we demonstrated that the reason for non-response to infliximab had implications for the treatment response to the next TNF inhibitor adalimumab, although it was necessary to adjust for the incidence of antibodies against adalimumab which interfered with the findings.10 Response to adalimumab was limited in switchers without anti-infliximab antibodies compared to patients who were anti-TNF naïve. The question was raised whether a second anti-TNF treatment should be offered to patients with RA who failed on initial treatment with anti-TNF, in the absence of anti-biological antibodies. The underlying mechanisms causing diminished response in patients who failed to respond despite the absence of anti-drug antibodies and optimal serum drug concentrations are not clear yet. It is possible that disease activity is TNF independent in these cases.15 It is likely that these patients will not respond to a subsequent TNF inhibitor.

The aim of the current study was to confirm our hypothesis that the reason for non-response (caused by immunogenicity or not) to a first TNF...
PATIENTS AND METHODS

Patients

Between December 2004 and October 2008, all consecutive patients with RA fulfilling the 1987 American College of Rheumatology criteria for RA and with a new etanercept prescription were included in an observational cohort at the Department of Rheumatology of the Jan van Breemen Institute. Treatment with etanercept was in accordance with the Dutch consensus statement on the initiation and continuation of TNF blocking treatment in RA, such as active disease indicated by a Disease Activity Score in 28 joints (DAS28) of >3.2 and failure on at least two disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) at a dosage of 25 mg weekly or at the maximal tolerable dosage. Patients were treated with either concomitant medication, including MTX and prednisone, or etanercept monotherapy. All patients used etanercept 50 mg subcutaneously every week or 25 mg twice a week. No 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.

All 292 consecutive patients with RA with a new prescription of etanercept were eligible for this study. Of these patients, 89 had previously been treated with either infliximab (n=30) or adalimumab (n=59), and are referred to as ‘switchers’.

Clinical response to etanercept

Disease activity was assessed at baseline and after 4, 16 and 28 weeks of treatment using DAS28, C reactive protein and erythrocyte sedimentation rate (ESR). Clinical response was assessed by the change in DAS28 score (ΔDAS28) and the European League Against Rheumatism (EULAR) response criteria. Additional data, such as changes in current medication use, was obtained at each visit. For the 89 switchers data regarding the first TNF inhibitor (clinical response, dosage and reason for discontinuing) were retrospectively obtained from the medical charts.

Measurement of antibodies against infliximab and adalimumab

The presence of anti-infliximab and anti-adalimumab antibodies was assessed at baseline prior to the start of etanercept. Antibodies against infliximab and adalimumab were measured using radioimmunoassay (RIA) as more extensively described previously. The assays measure specific high avid IgG antibodies by an antigen binding test. Test results were converted into arbitrary units per ml (AU/ml) by comparison with dilutions of a reference serum. Recently, patient sera were tested in a bioassay, which confirmed the specificity and validity of the RIA. The mean cut-off value was set at 12 AU/ml, which was derived from 100 healthy donors. Assay specificity was demonstrated by the absence of anti-adalimumab in 25 sera containing high-titre anti-infliximab antibodies. In the assays we did not find cross-reactivity.

Statistical analysis

Data are shown as mean (SD), median (IQR), or percentages. The distribution of variables was tested for normality and transformed if necessary. Differences between switchers and patients who were TNF naive were evaluated by using an independent t test, or when appropriate Mann–Whitney test or Pearson’s χ2 test for dichotomous variables. Last observation carried forward data was used for patients who discontinued the treatment with etanercept before 28 weeks. To determine whether confounders modified the relation between changes in DAS28 and previous biological use multiple regression analysis was performed. All baseline variables were considered as potential confounders and included in the regression model if the β changed 10% or more. p Values <0.05 were considered statistically significant. All analyses were performed using SPSS V.16.0 (SPSS, Chicago, Illinois, USA).

Table 1 Demographic and clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All patients (n=292)</th>
<th>Biological naive (n=203)</th>
<th>Switchers (n=89)</th>
<th>Switchers with anti-drug antibodies (n=47)</th>
<th>Switchers without anti-drug antibodies (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.8 ± 12.7</td>
<td>52.6 ± 12.5</td>
<td>53.4 ± 13.4</td>
<td>52.5 ± 14.2</td>
<td>54.4 ± 12.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>239 (82)</td>
<td>161 (79)</td>
<td>78 (88)</td>
<td>41 (87)</td>
<td>37 (88)</td>
</tr>
<tr>
<td>DMARD treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior DMARDs</td>
<td>2.9 ± 1.3</td>
<td>2.8 ± 1.2</td>
<td>3.3 ± 1.4*</td>
<td>3.3 ± 1.4</td>
<td>3.14 ± 1.4</td>
</tr>
<tr>
<td>MTX dose, mg/week</td>
<td>19.7 ± 7.0</td>
<td>20.6 ± 6.7</td>
<td>17.3 ± 7.5*</td>
<td>15.7 ± 7.4</td>
<td>18.8 ± 7.4</td>
</tr>
<tr>
<td>Prednisolone dose, mg/day</td>
<td>8.2 ± 3.8</td>
<td>7.7 ± 3.6</td>
<td>9.2 ± 4.4</td>
<td>9.6 ± 5.1</td>
<td>8.5 ± 2.9</td>
</tr>
<tr>
<td>Other DMARD than MTX, n (%)</td>
<td>96 (33)</td>
<td>81 (40)</td>
<td>15 (17)*</td>
<td>9 (19)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8 (3–16)</td>
<td>6 (2–15)</td>
<td>12 (6–17)*</td>
<td>14 (9–18)</td>
<td>10 (5–17)</td>
</tr>
<tr>
<td>Rheumatoid factor positive, n (%)</td>
<td>207 (72)</td>
<td>140 (70)</td>
<td>67 (75)</td>
<td>38 (61)</td>
<td>29 (69)</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
<td>207 (72)</td>
<td>135 (67)</td>
<td>72 (61)*</td>
<td>42 (89)</td>
<td>30 (71)</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.2 ± 1.3</td>
<td>5.2 ± 1.3</td>
<td>5.3 ± 1.3</td>
<td>5.5 ± 1.2</td>
<td>5.0 ± 1.4</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>23 (11–40)</td>
<td>21 (10–38)</td>
<td>27 (16–45)*</td>
<td>28 (15–46)</td>
<td>27 (15–42)</td>
</tr>
<tr>
<td>C reactive protein, mg/litre</td>
<td>8 (3–21)</td>
<td>7 (3–21)</td>
<td>10 (3–21)</td>
<td>14 (4–27)</td>
<td>8 (3–13)</td>
</tr>
</tbody>
</table>

Mean values ± SD, median and IQR, or percentages are shown.

*There were significant differences between patients who were anti-TNF naive and switchers for prior DMARDs (p<0.003), MTX use (p=0.028), MTX dose (p=0.001), other DMARDs than MTX (p<0.001), disease duration (p<0.001), erosive disease (p=0.011) and erythrocyte sedimentation rate (p=0.027).

†There was a significant difference between switchers with and without antibodies for MTX use (p=0.031).
RESULTS
Patient characteristics
Baseline characteristics before the start of etanercept treatment are shown in table 1.

Of the 292 patients, 89 patients had previously been treated with either infliximab (n=30) or adalimumab (n=59). Eight of these patients had received infliximab and adalimumab prior to the start with etanercept. The median time use of the prior biological was significantly longer for patients treated with infliximab compared to adalimumab (33 (15–49) months vs 9 (6–17) months, p<0.001). There were no other differences between prior infliximab and adalimumab users. The median dosage of infliximab was 7.5 (5–10) mg/kg. 19 patients had used infliximab in a dosage more than 5 mg/kg. A total of 20 adalimumab switchers had used adalimumab 40 mg every week instead of every other week. The mean DAS28 change for all switchers on their first TNF inhibitor was 0.62±1.5. Of 89 patients, 76 had stopped their first biological due to inefficacy, determined using the EULAR criteria for non-response, 12 patients due to adverse events and 1 patient due to a pregnancy wish. A total of 52% of the patients who had stopped infliximab or adalimumab due to inefficacy had been non-responders since the start of the treatment and 68% had lost an initial response. The median interval between stopping the previous biological and starting etanercept was 4 weeks (IQR 2–24).

After 16 weeks of etanercept treatment 276 (95%) patients were still on treatment, and 234 (80%) completed 28 weeks of the observation period. Of the 58 patients who discontinued etanercept treatment before 28 weeks 35 (60%) patients stopped due to inefficacy, and 8 (14%) patients were lost to follow-up. Of the 58 patients who stopped etanercept treatment before 28 weeks, 22 (38%) were switchers, of whom 13 patients had antibodies against previously used infliximab or adalimumab. There were no significant differences between patients who discontinued etanercept treatment within 6 months and patients who stayed on treatment (data not shown).

Clinical response
After 16 weeks of etanercept treatment the mean change in DAS28 for all patients was 1.7±1.4. According to the EULAR response criteria 97 (35%) patients were good, 113 (41%) were moderate and 66 (24%) were non-responders. After 28 weeks of etanercept treatment the mean change in DAS28 was 1.9±1.4. And 97 (42%) patients were good, 102 (44%) were moderate and 35 (15%) were EULAR non-responders. When the group of patients who were TNF naive was compared to the group of switchers the mean change in DAS28 was significantly lower in the switchers group (ΔDAS28 2.1±1.3 vs 1.6±1.3; p=0.015) after 28 weeks of etanercept treatment (table 2).

Correction for confounding variables disease duration, DAS28 baseline and ESR at baseline did not change the results (95% CI −0.791 to −0.154; p=0.004). Also, the EULAR response was different between both groups. Among patients who were TNF naive 47% were good, 40% were moderate and 13% were non-responders compared to 27% good, 52% moderate and 21% non-responders in the switchers group (p=0.005).

In the post hoc analysis only the percentage of good responders was significantly different between patients who were anti-TNF naive and switchers (p=0.004).

Immunogenicity in relation to clinical response
Out of 89 switchers, 47 patients (53%) had antibodies against adalimumab or infliximab as measured at baseline prior to the start of etanercept treatment. Patients with detectable anti-drug antibodies had significantly lower doses of MTX at baseline compared to patients without antibodies (p=0.031). There were no other baseline differences between these patients (table 1).

When patients who were anti-TNF naive were compared to switchers without antibodies the DAS28 improvement was significantly larger in patients who were anti-TNF naive (ΔDAS28 2.1±1.3 vs 1.2±1.3; p=0.001) after 28 weeks of etanercept treatment. Correction for the confounding variable DAS28 at baseline did not change the results (95% CI −1.175 to −0.341; p=0.016). There was no significant difference in the improvement in DAS28 between patients who were TNF naive compared to switchers with antibodies (ΔDAS28 2.1±1.3 vs 2.0±1.3; p=0.743). Improvement in DAS28 was significantly larger in switchers with anti-drug antibodies compared to switchers without antibodies (ΔDAS28 2.0±1.3 vs 1.2±1.3; p=0.017) (table 2). Correction for confounding variable DAS28 at baseline (95% CI −0.434 to −0.044; p=0.016) did not change this (figure 1).

Figure 1 The improvement in 28 joint Disease Activity Score (DAS28) in patients who were tumour necrosis factor (TNF)-naive versus switchers with and without antibodies. The grey bars represent changes in DAS28 (mean values + SD) after 28 weeks of etanercept treatment in patients who were TNF naive, switchers with and without antibodies, respectively.

Table 2 Baseline, follow-up and change in DAS28 after 6 months etanercept treatment

<table>
<thead>
<tr>
<th></th>
<th>DAS28 at baseline</th>
<th>DAS28 after 6 months</th>
<th>ΔDAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=292)</td>
<td>5.2 ± 1.3</td>
<td>3.3 ± 1.3</td>
<td>1.9 ± 1.4</td>
</tr>
<tr>
<td>Patients who were biological naive (n=203)</td>
<td>5.2 ± 1.3</td>
<td>3.1 ± 1.2</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Switchers (n=89)</td>
<td>5.3 ± 1.3</td>
<td>3.7 ± 1.3</td>
<td>1.6 ± 1.4</td>
</tr>
<tr>
<td>Switchers with anti-drug antibodies (n=47)</td>
<td>5.5 ± 1.2</td>
<td>3.5 ± 1.0</td>
<td>2.0 ± 1.3</td>
</tr>
<tr>
<td>Switchers without anti-drug antibodies (n=42)</td>
<td>5.0 ± 1.4</td>
<td>3.8 ± 1.5</td>
<td>1.2 ± 1.3</td>
</tr>
</tbody>
</table>

Mean values ± SD are shown.
DAS28, Disease Activity Score in 28 joints.
Also, the EULAR response was different between switchers with and without antibodies. Among switchers with antibodies 29% were good, 62% were moderate and 9% were non-responders compared to 24% good, 43% moderate and 33% non-responders in the switchers without antibodies. In the post hoc analysis only the percentage of EULAR non-responders was different between two groups (p=0.014).

**DISCUSSION**

This study demonstrates that patients who previously discontinued infliximab or adalimumab treatment and who had antibodies against these drugs achieved a clinical response after switching to etanercept that did not differ from patients who were anti-TNF naïve. In contrast, switchers without antibodies against adalimumab or infliximab had a significantly lower response to etanercept compared to switchers with antibodies and patients who were TNF naïve. Previously, we showed that response to adalimumab was limited in switchers without anti-infliximab antibodies compared to switchers with anti-infliximab antibodies. We hypothesised that there were different types of non-responders with different underlying mechanisms causing non-response. The results of the current study confirm this hypothesis.

Our results are in accordance with other studies reporting a diminished response on the second-course TNF inhibitor in a subpopulation of patients with RA. This subpopulation was defined in these studies as a group of primary non-responders; these patients experienced no clinical benefit since the start of the treatment and switching to another TNF inhibitor did not contribute to improvement of disease activity. The mechanisms of primary non-response to TNF blocking agents are still poorly understood. Recent research has shown an association between low expression of TNFα in the serum and synovial fluid and a diminished clinical response to the TNF inhibitor infliximab. It is possible that TNF is not the main cytokine instigating disease activity in these patients. In contrast with our results a recently published study stated that the reason for discontinuation of the first TNF blocking agent does not influence the effect of a second TNF blocking agent. In this study antibodies against TNF agents were not determined and patients were divided into groups based on clinical data. In our opinion, it is not possible to differentiate into different types of non-responders based on clinical data only. We argue that it is necessary to measure immunogenic response to determine the reason for non-response in a patient.

The formation of neutralising antibodies against adalimumab and infliximab is associated with the loss of previously achieved clinical response and is one of the reasons for secondary non-response. Anti-etanercept antibodies were not detected or only in a low number of patients without influence on efficacy or adverse events. The factors predicting immunogenicity are diverse. Anti-adalimumab and anti-infliximab antibodies are usually directed against the idiotype or functional part of the therapeutic molecule. That leads to the neutralisation of adalimumab or infliximab. In addition to the structure of the molecule the prevalence of human anti-chimaeric antibodies and human anti-human antibodies is inversely associated with dose and additional use of immunosuppressive treatment. Our data confirmed this, as switchers with antibodies had lower doses of MTX than switchers without antibodies.

Due to the observational cohort design potential biases should be taken into account. The decision to start a second biological was determined by the treating rheumatologist and can lead to a potential selection bias. Furthermore, despite adjustment for known confounders we were not able to exclude confounding by unmeasured factors, for instance x-ray damage, functional disability and the use of self-medications such as analgesics. In addition to possible unmeasured confounders, there were differences in baseline characteristics. Switchers had longer disease duration, more prior DMARDs, more erosive disease, higher ESR values, lower MTX doses and less concomitant other DMARDs than MTX. It is possible that switchers had more severe disease than patients who were anti-TNF naïve, which would presumably make it more difficult to detect a clinical improvement. However, improvement in DAS28 did not differ between switchers with antibodies and patients who were TNF naïve. Furthermore, we performed a confounding analysis considering all variables and this did not alter the results. The strengths of this study are a one-centre based cohort design reflecting the heterogeneous population of the true daily practice and a systematic prospective assessment of a broad range of disease characteristics.

The results of the current study underline the importance of therapeutic drug monitoring, which includes disease activity assessment and drug levels and anti-drug antibody measurement. Patients who failed their first-course TNF inhibition due to another reason than an immunogenic anti-drug reaction will probably benefit from switching to a therapeutic with a different mechanism of action. Furthermore, the results of this study show that in patients who were non-responding with an immunogenic response against TNF inhibitors the response to a second TNF inhibitor, etanercept, did not differ from patients who were TNF naïve. The UK National Institute for Health and Clinical Excellence (NICE) guidelines does not recommend sequential use of TNF blocking agents, except when adverse events were the reason for discontinuation. Therefore by following NICE guidelines a substantial group of patients would be excluded from a beneficial treatment with the second-course TNF inhibitor. Determining the immunogenic status of a patient who is non-responding can be part of a personalised treatment regimen. It can be very helpful in deciding in which patients switching could be beneficial and meaningful considering the high costs of anti-TNF treatment.

**Acknowledgements** The authors are grateful to the Clinical Research Bureau of the Jan van Breemen Institute, which receives support from the Dutch Arthritis Foundation, for help in the conduct of the study. The authors thank the research nurses Marga Kammiej-Rippen, Anne-Marie Abrahams, Martine Kos and Nina Kivist for performing clinical assessments. Finally, authors wish to thank Henk van Vrie and Margret de Koning for preparation and performing the assays.

**Funding** The clinical part of this study was partially financed by Wyeth Pharmaceuticals. In addition, this investigation was also facilitated by the Clinical Research Bureau of the Jan van Breemen Institute.

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the METC slotervaart ziekenhuis.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**REFERENCES**


