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Chapter 6

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 is to test the hypothesis that the reason for non-response (caused by immunogenicity or not) to a first TNF-inhibitor defines whether a second TNF-inhibitor will be effective.

Methods. This cohort study consisted of 292 consecutive RA patients, all treated with etanercept. Eighty-nine 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 anti-TNF naive patients were assessed after 28 weeks of therapy using changes in DAS28.

Results. After 28 weeks of therapy response to etanercept did not differ between anti-TNF naive patients and switchers with anti-drug antibodies (Δ DAS28=2.1 \pm 1.3 versus Δ DAS28=2.0 \pm 1.3; P=0.743). In contrast, switchers without anti-drug antibodies had a diminished response to etanercept treatment compared to both TNF naive patients (Δ DAS28=1.2 \pm 1.3 versus Δ DAS28=2.1 \pm 1.3; P=0.001) and switchers with antibodies (Δ DAS28=2.0 \pm 1.3 versus Δ DAS28=1.2 \pm 1.3; P=0.017).

Conclusion. RA patients with an immunogenic response against a first TNF-blocking agent had a better clinical response to a subsequent TNF-blocker compared to RA patients 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 personalized treatment regimen.

INTRODUCTION

Tumor 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 revolutionized treatment for RA. Currently, infliximab, adalimumab and etanercept are widely used for the treatment of RA.[1] They are biologically active molecules, varying from chimeric to humanized 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 rheumatoid arthritis (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) which 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 i.e. switching to another TNF-inhibitor, switching to a biological with another mechanism of action (for example 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 anti-TNF naive patients.[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 showed 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 anti-TNF naive patients. The question was raised whether a second anti-TNF therapy should be offered to RA-patients 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. Possibly 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 is to confirm our hypothesis that the reason for non-response (caused by immunogenicity or not) to a first TNF inhibitor has implications for treatment response to the next TNF inhibitor in a cohort of etanercept treated RA patients. Clinically relevant antibodies against etanercept have not been detected.[16;17] We expect that the outcome of this study will be more pronounced since clinical response to etanercept treatment is not obscured by immunogenicity.

PATIENTS AND METHODS

Patients. Between December 2004 and October 2008, all consecutive RA patients, fulfilling the 1987 ACR 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 to the Dutch consensus statement on the initiation and continuation of TNF blocking

therapy 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 anti-rheumatic drugs (DMARDs) including methotrexate (MTX) at a dosage of 25 mg weekly or at the maximal tolerable dosage.[18] 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. None of patients received dose increase of etanercept during the six 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 RA patients with a new prescription etanercept were eligible for this study. Eighty nine of these patients 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 therapy using DAS28, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Clinical response was assessed by the change in DAS28 score (Δ DAS28) and the European League Against Rheumatism (EULAR) response criteria.[19] 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 radio immunoassay (RIA) as more extensively described previously.[2;4;5] The assays measure specific high avid IgG antibodies by an antigen binding test. Test results were converted into arbitrary units per millilitre (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.[2] 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.[2]

Statistical analysis. Data are shown as mean (SD), median (interquartile ranges (IQR)) or percentages. The distribution of variables was tested for normality and transformed if necessary. Differences between switchers and TNF-naive patients were evaluated by using an independent t-test, or when appropriate Mann-Whitney test or Pearson's chi-square test for dichotomous variables. Last observation carried forward (LOCF) 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 beta changed 10% or more. P values <0.05 were considered statistically significant. All analyses were performed using SPSS version 16.0.

RESULTS

Patient characteristics. Baseline characteristics before the start of etanercept treatment are shown in Table 1.

Table 1. Demographic and clinical characteristics at baseline

	all patients (n = 292)	biological naive (n=203)	switchers (n=89)	switchers with anti-drug antibodies (n = 47)	switchers without anti- drug antibodies (n = 42)
Demographics					
Age	52.8 ± 12.7	52.6 ± 12.5	53.4 ± 13.4	52.5 ± 14.2	54.4 ± 12.4
Female, no, (%)	239 (82)	161 (79)	78 (88)	41 (87)	37 (88)
DMARD therapy					
Prior DMARDs	2.9 ± 1.3	2.8 ± 1.2	3.3 ± 1.4*	3.3 ± 1.4	3.14 ± 1.4
Methotrexate use, no, (%)	223 (76)	162 (80)	61 (69)*	29 (62)	32 (76)#
Methotrexate dose (mg/wk)	19.7 ± 7.0	20.6 ± 6.7	17.3 ± 7.5*	15.7 ± 7.4	18.8 ± 7.4
Prednisolon use, no, (%)	84 (29)	57 (28)	27 (30)	17 (36)	10 (24)
Prednisolon dose (mg/day)	8.2 ± 3.8	7.7 ± 3.6	9.2 ± 4.4	9.6 ± 5.1	8.5 ± 2.9
Other DMARD than MTX, no, (%)	96 (33)	81 (40)	15 (17)*	9 (19)	6 (14)
Disease status					
Disease duration (years)	8 (3-16)	6 (2-15)	12 (8-17)*	14 (9-18)	10 (5-17)
Rheumatoid factor positive, no. (%)	207 (72)	140 (70)	67 (75)	38 (81)	29 (69)
Erosive disease, no. (%)	207 (72)	135 (67)	72 (81)*	42 (89)	30 (71)
DAS28	5.2 ± 1.3	5.2 ± 1.3	5.3 ± 1.3	5.5 ± 1.2	5.0 ± 1.4
Erythrocyte sedimentation rate (mm/h)	23 (12-40)	21 (10-38)	27 (16-45)*	28 (15-46)	27 (15-42)
C-reactive protein (mg/l)	8 (3-21)	7 (3-21)	10 (3-21)	14 (4-27)	8 (3-13)

Mean values ± SD, median and interquartile range, or percentages are shown. DMARDs = disease modifying antirheumatic drugs. DAS28 = disease activity score in 28 joints.

*There were significant differences between anti-TNF naive patients and switchers for prior DMARDs (P= 0.003), methotrexate use (P= 0.028), methotrexate 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 methotrexate use (P= 0.031).

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 both infliximab and adalimumab prior to the start with etanercept. The median time use of the prior biological was significantly longer for infliximab treated patients compared to adalimumab (33 (15-49) vs 9(6-17) p< 0.001). There were no other differences between prior infliximab and adalimumab users. The median dosage of infliximab was 7.5 (3-10), 19 patients had used infliximab in a dosage more than 3 mg/kg. Twenty 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 . Seventy six patients out of 89 had stopped their first biological due to inefficacy, determined using the EULAR criteria for non-response, 12 patients due to adverse events and one patient due to a pregnancy wish. Thirty-two percent 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 time interval between stopping the previous biological and starting etanercept was 4 weeks, interquartile range (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 fifty eight patients who discontinued etanercept treatment before 28 weeks 35 (60%) patients stopped due to inefficacy, 15 (26%) because of adverse events and 8 (14%) patients were lost to follow-up. Out of the 58 patients who stopped etanercept treatment before 28 weeks 22 (38%) were switchers, from 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 TNF-naive patients was compared to the group of switchers the mean change in DAS28 was significantly lower in the switchers group (Δ DAS28 2.1 ± 1.3 versus 1.6 ± 1.4 , $P= 0.015$) after 28 weeks of etanercept treatment.(Table 2.)

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

	DAS28 at baseline	DAS28 after 6 months	Δ DAS28
All patients (n=292)	5.2 ± 1.3	3.3 ± 1.3	1.9 ± 1.4
Biological naive patients (n=203)	5.2 ± 1.3	3.1 ± 1.2	2.1 ± 1.3
Switchers (n=89)	5.3 ± 1.3	3.7 ± 1.3	1.6 ± 1.4
Switchers with anti-drug antibodies (n=47)	5.5 ± 1.2	3.5 ± 1.0	2.0 ± 1.3
Switchers without anti-drug antibodies (n=42)	5.0 ± 1.4	3.8 ± 1.5	1.2 ± 1.3

Mean values \pm SD are shown.

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

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 ($P= 0.014$).

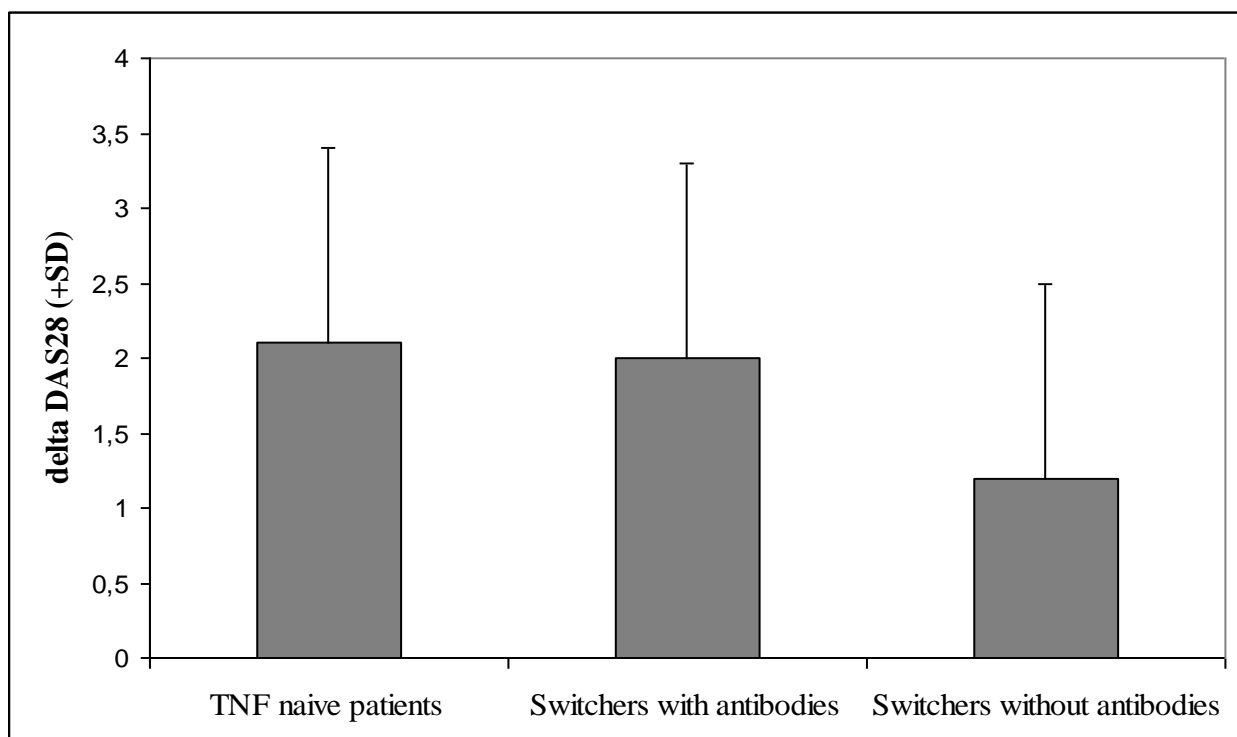


Figure 1. The improvement in DAS28 in TNF naive patients versus switchers with and without antibodies. The grey bars represents changes in DAS28 (mean values +SD) after 28 weeks of etanercept treatment in TNF naïve patients, switchers with and without antibodies, respectively.

DISCUSSION

This study demonstrates that patients who had previously discontinued treatment with infliximab or adalimumab and had antibodies against these drugs achieved a clinical response after switching to etanercept that did not differ from anti-TNF naïve patients. In contrast, switchers without antibodies against adalimumab or infliximab had a significantly lower response to etanercept compared to both

switchers with antibodies and TNF-naïve patients. Previously, we showed that response to adalimumab was limited in switchers without anti-infliximab antibodies compared to switchers with anti-infliximab antibodies.[10] We hypothesized 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 RA patients.[8;9] 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 TNF α in the serum and synovial fluid and a diminished clinical response to the TNF-inhibitor infliximab.[15;20] 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.[21] 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 neutralizing 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.[3-5;22] Anti-etanercept antibodies were not detected or only in a low number of patients without influence on efficacy or adverse events.[16;17] 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 neutralization of adalimumab or infliximab. In addition to the structure of the molecule the prevalence of human antichimeric antibodies (HACA) and human antihuman antibodies (HAHA) is inversely associated with dose and additional use of immunosuppressive therapy.[23] 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 anti-TNF naïve patients, which would presumably make it more difficult to detect a clinical improvement. However, improvement in DAS28 did not differ between switchers with antibodies and TNF naïve patients. 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 not only disease activity assessment but also 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.[24;25] Furthermore, the results of this study show that in non-responding patients with an immunogenic response against TNF-inhibitors the response to a second TNF inhibitor, etanercept, did not differ from TNF naive patients. The UK National Institute for Health and Clinical Excellence (NICE) guidance does not recommend sequential use of TNF blocking agents, except when adverse events were the reason for discontinuation.[26]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 non-responding patient can be part of a personalized treatment regimen. It can be very helpful in deciding in which patient switching could be beneficial and meaningful considering the high costs of anti-TNF therapy.

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