Comparison of Long-Term Clinical Outcome With Etanercept Treatment and Adalimumab Treatment of Rheumatoid Arthritis With Respect to Immunogenicity

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Objective. **To compare rates of sustained low and minimal disease activity and remission according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria during 3-year followup in rheumatoid arthritis (RA) patients treated with etanercept and adalimumab in routine care.**

Methods. **Four hundred seven RA patients previously unexposed to tumor necrosis factor antagonists were treated with etanercept (n = 203) or adalimumab (n = 204) and assessed at 3- and later 6-month intervals. Treatment allocation was at the discretion of the treating rheumatologist. Clinical parameters were measured at each time point, as were anti-adalimumab antibodies in adalimumab-treated patients. Achievement of clinical outcome was defined as the occurrence of sustained (at least 12 consecutive months) low dis-ease activity (28-joint Disease Activity Score [DAS28] <3.2), minimal disease activity (DAS28 <2.6), or ACR/EULAR remission based on the Simplified Disease Activity Index (SDAI). Non-overlapping response rates were calculated.**

Results. **Among the adalimumab group, 13% reached sustained low disease activity but not sustained minimal disease activity, 15% reached sustained minimal disease activity but not sustained remission according to the SDAI, and 16% reached sustained ACR/EULAR remission. In the etanercept group the corresponding rates were 16%, 11%, and 12%, respectively (*P* = 0.42, overall test for linear trend). Adalimumab-treated patients without anti-adalimumab antibodies (n = 150 [74%]) had the best outcomes, and adalimumab-treated patients with anti-adalimumab antibodies the worst, with outcomes in etanercept-treated patients in between (*P* < 0.0001). Differences were most apparent in the sustained SDAI remission and sustained minimal disease activity categories. For example, 40% of anti-adalimumab antibody–negative patients, 23% of etanercept-treated patients, and 4% of anti-adalimumab antibody–positive patients achieved at least sustained minimal disease activity.**

Conclusion. **Overall, etanercept and adalimumab treatment appear similar in inducing a good long-term clinical outcome. However, in the case of adalimumab this is strongly dependent on the presence or absence of anti-adalimumab antibodies.**

In the last decade, treatment with tumor necrosis factor (TNF) inhibitors has significantly improved the outcome in patients with rheumatoid arthritis (RA) that has not responded to conventional disease-modifying antirheumatic drug (DMARD) therapy (1). However, to date there are no reported randomized head-to-head

trials comparing efficacy, safety, and adherence rates between the most frequently used TNF inhibitors (etanercept, adalimumab, and infliximab). In meta-analyses, indirect comparison revealed no significant difference between the 3 TNF inhibitors (2,3).

Results from large registries of biologic agent–treated patients are inconsistent. In the DREAM (Dutch Rheumatoid Arthritis Monitoring registry) study, 707 patients receiving their first TNF inhibitor were followed up for 1 year. Response to adalimumab and etanercept treatment was similar, but higher than response to infliximab treatment (4). Results were similar in the Danish DANBIO registry study comprising 2,326 anti-TNF–naive patients (1). However, whereas adalimumab induced higher rates of European League Against Rheumatism (EULAR) response (5) and remission at 6 months compared to etanercept, the latter had a significantly higher drug adherence rate after 4 years compared to both adalimumab and infliximab (1).

In the above studies, pharmacokinetic aspects of the treatment, such as presence of antidrug antibodies, were not taken into account. Recently, we demonstrated that in our adalimumab-treated RA patient cohort the development of anti-adalimumab antibodies significantly influenced treatment outcome (6). Patients who developed anti-adalimumab antibodies during a 3-year time period were less likely to achieve minimal disease activity or remission, and treatment failure occurred more often compared with patients without anti-adalimumab antibodies. Anti-etanercept antibodies have also been reported in low prevalence, but their clinical relevance has not been demonstrated (7,8). In contrast, we were unable to detect neutralizing anti-etanercept antibodies; however, higher serum etanercept levels correlated with better clinical outcome (9).

In the current analysis of our cohorts (6,9) we compared the rates of sustained American College of Rheumatology (ACR)/EULAR remission (10), minimal disease activity, and low disease activity in etanercept- and adalimumab-treated RA patients during 3 years of followup. In the patients who were treated with adalimumab, we investigated the relationship of these rates to the presence of anti-adalimumab antibodies.

PATIENTS AND METHODS

Patients. The patients for the current analysis were selected from our simultaneously running observational prospective cohorts at the rheumatology department of the Jan van Breemen Research Institute | Reade. Two hundred ninety-two patients were included in the etanercept cohort and

272 patients in the adalimumab cohort (6,9). Treatment allocation was at the discretion of the treating rheumatologist. Briefly, inclusion criteria for these cohorts were as follows: RA according to the ACR 1987 criteria (11), and active disease indicated by a 28-joint Disease Activity Score (DAS28) (12) of ≥3.2 despite earlier treatment with at least 2 DMARDs including methotrexate at a dosage of 25 mg weekly or at the maximally tolerable dosage, according to the Dutch consensus statement on the initiation and continuation of TNF blocking therapy in RA (13).

Only data from anti-TNF–naive patients were used in the current study, and therefore 407 patients were enrolled. Two hundred four of these patients were treated with adalimumab and 203 were treated with etanercept. Patients were treated either with adalimumab/etanercept and concomitant DMARD therapy or prednisone or with adalimumab/etanercept monotherapy. All patients received adalimumab 40 mg subcutaneously every other week or etanercept 50 mg subcutaneously weekly or 25 mg subcutaneously twice weekly. The study was approved by the local medical ethics committee, and all patients provided written informed consent.

Clinical response. Disease activity was assessed, using the DAS28, at baseline and after 4, 16, 28, 40, 52, 78, 104, 130, and 156 weeks of therapy. Achievement of clinical outcome was defined as the occurrence of sustained (at least 12 consecutive months) low disease activity (DAS28 <3.2), minimal disease activity (DAS28 <2.6), or remission based on the Simplified Disease Activity Index (SDAI) (14), according to the ACR/EULAR criteria.

Measurement of adalimumab concentrations and antidrug antibodies. Serum samples were collected just prior to injection of adalimumab or etanercept at baseline and after 4, 16, 28, 40, 52, 78, 104, 130, and 156 weeks. The presence of antidrug antibodies was determined at all study time points between baseline and 156 weeks. Anti-adalimumab antibodies were detected by radioimmunoassay. For measurement of anti-etanercept antibodies, several assays were used; these assays have been described previously (9). Trough serum adalimumab concentrations were measured by enzyme-linked immunosorbent assay (6). Patients were considered positive for anti-adalimumab antibodies if the titer was >12 arbitrary units/ml on at least 1 occasion, in combination with a serum adalimumab level of <5.0 mg/liter. The cutoff was set at 5 mg/liter because higher drug levels interfere with the results of the radioimmunoassay (15). All baseline samples obtained before the start of treatment were negative. As noted above and previously reported (9), we were unable to detect (neutralizing) anti-etanercept antibodies in this cohort.

Statistical analysis. The significance of differences in baseline characteristics between patients in the etanercept and adalimumab groups was assessed by t-test for independent samples, chi-square test, or Mann-Whitney U test as appropriate. P values (2-sided) less than 0.05 were considered significant. For patients who did not complete 3 years of followup, data through the last available visit were analyzed; no imputation methods were used. To avoid spurious statistical testing we calculated non-overlapping rates of the different outcome categories (16) in etanercept- and adalimumab-treated patients and tested the overall difference in rates by chi-square test for linear trend. Thereafter, post hoc analysis was used to compare 3 groups: etanercept-treated patients,

anti-adalimumab antibody–positive adalimumab-treated patients, and anti-adalimumab antibody–negative adalimumab-treated patients. Ordinal logistic regression was used to test for potential confounding for the overall difference in non-overlapping response rates. All baseline characteristics with available information were considered as potential confounders and determined for every analysis. Variables were included in the regression model as confounders if the beta changed by ≥10% after inclusion of the variable. SPSS for Windows, version 16.0 was used for statistical analysis.

RESULTS

Baseline clinical and demographic characteristics of the 407 patients are shown in Table 1. C-reactive protein levels were higher in patients starting adalimumab treatment than in those starting etanercept treatment (median [interquartile range] 12 mg/liter [6–27] versus 7 mg/liter [3–21]); $P = 0.003$.

Of the adalimumab-treated patients 58% (n = 119) completed 3 years of followup, versus 55% (n = 112) of the etanercept-treated patients ($P = 0.528$). The median duration of treatment was 143 weeks (interquartile range 43–156) and 130 weeks (interquartile range 28–156) in the adalimumab and etanercept groups, respectively. There were no differences in reasons for treatment discontinuation between treatment groups. Of the total of 176 patients who dropped out of the study, 96 (54%) withdrew due to treatment inefficacy, 31 (18%) because of adverse events, 7 (4%) because of a combination of treatment inefficacy and adverse events, and 42 (24%) for other reasons (clinical remission [n = 5], relocation [n = 15], unwillingness to participate [n = 13], and loss to followup [n = 9]).

Of the adalimumab-treated patients, 13% (n = 27) reached sustained low disease activity but not sustained minimal disease activity, 15% (n = 30) reached sustained minimal disease activity but not sustained SDAI remission, and 16% (n = 32) reached sustained SDAI remission. Of the etanercept-treated patients, 16% (n = 32) reached sustained low disease activity but not sustained minimal disease activity, 11% (n = 22) reached sustained minimal disease activity but not sustained SDAI remission, and 12% (n = 25) reached sustained SDAI remission ($P = 0.42$) (Figure 1). Sensitivity analysis was used to test whether the reason for discontinuation corresponded with the clinical outcome. This analysis showed that all patients who discontinued treatment due to inefficacy were classified in the nonresponse group, and all who discontinued due to remission were classified in the sustained SDAI remission group.

Fifty-four (26%) of the adalimumab-treated patients developed anti-adalimumab antibodies during treatment. Of these 54 anti-adalimumab antibody–positive patients, 13% (n = 7) reached sustained low disease activity but not sustained minimal disease activity, none reached sustained minimal disease activity but not sustained SDAI remission, and 4% (n = 2) reached sustained SDAI remission. Thirteen percent (n = 20), 20% (n = 30), and 20% (n = 30) of the

Table 1. Baseline characteristics of the RA patients studied*

Characteristic	All patients (n = 407)	Etanercept group (n = 203)	Adalimumab group (n = 204)
Age, mean ± SD years	53 ± 12	53 ± 13	54 ± 12
Female, no. (%)	317 (78)	161 (79)	156 (76)
Disease duration, median (IQR) years	6.8 (2.3–15.0)	6.0 (2.0–14.5)	7 (3–16)
IgM-RF positive, no. (%)	285 (70)	140 (69)	145 (71)
Erosive disease, no. (%)	286 (70)	135 (67)	151 (74)
DAS28, mean ± SD	5.2 ± 1.3	5.2 ± 1.3	5.1 ± 1.2
SDAI, mean ± SD	29.3 ± 12.5	29.6 ± 13.3	28.9 ± 11.7
ESR, median (IQR) mm/hour	21 (11–38)	21 (10–38)	22 (11–40)
CRP, median (IQR) mg/liter	10 (4–22)	7 (3–21)	12 (6–27)†
No. of prior DMARDs, mean ± SD	2.9 ± 1.2	2.8 ± 1.2	2.9 ± 1.2
Current MTX use, no. (%)	319 (78)	162 (80)	157 (77)
MTX dosage, mean ± SD mg/week	20.7 ± 6.6	20.6 ± 6.7	20.8 ± 6.6
Current prednisone use, no. (%)	122 (30)	57 (28)	65 (32)
Prednisone dosage, mean ± SD mg/day	7.6 ± 4.1	7.7 ± 3.6	7.6 ± 4.6

* RA = rheumatoid arthritis; IQR = interquartile range; IgM-RF = IgM rheumatoid factor; DAS28 = 28-joint Disease Activity Score; SDAI = Simplified Disease Activity Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate.
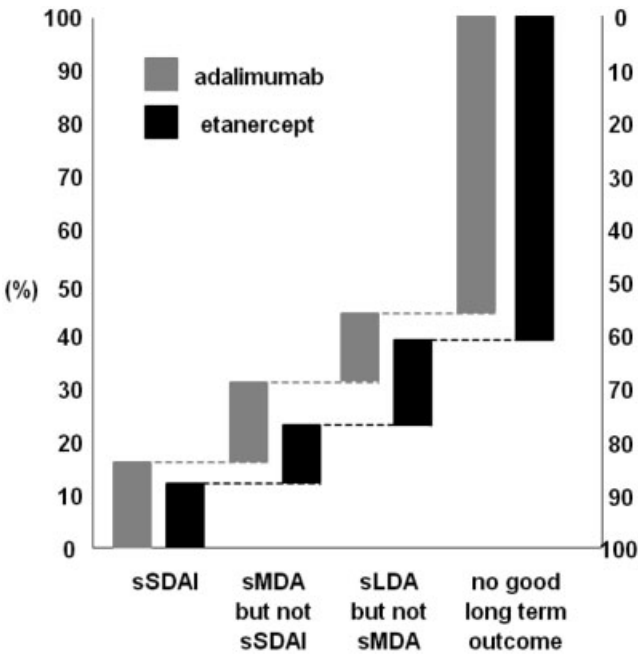† $P = 0.003$ versus etanercept group.

Figure 1. Non-overlapping outcome rates in the adalimumab and etanercept cohorts. There was no statistically significant difference in the rates of the different outcomes between adalimumab- and etanercept-treated patients ($P = 0.42$). sSDAI = sustained American College of Rheumatology/European League Against Rheumatism remission based on the Simplified Disease Activity Index; sMDA = sustained minimal disease activity; sLDA = sustained low disease activity.

150 anti-adalimumab antibody–negative adalimumab-treated patients reached sustained low disease activity but not sustained minimal disease activity, sustained minimal disease activity but not sustained SDAI remission, and sustained SDAI remission, respectively. Overall non-overlapping response rates differed significantly between the etanercept group and both the anti-adalimumab antibody–negative and anti-adalimumab antibody–positive adalimumab groups (Figure 2 and Table 2).

Ordinal logistic regression analysis to correct for potential confounders did not change the results (Table 3). The odds ratios shown in Table 3 indicate the odds of etanercept-treated patients reaching a higher/better clinical response versus the odds of adalimumab-treated patients (with or without anti-adalimumab antibodies) reaching a higher/better clinical outcome. Overall, treatment response was comparable between etanercept- and adalimumab-treated patients (adjusted odds ratio 0.81 [95% confidence interval 0.54–1.21]) (which can be interpreted as no difference between etanercept- and
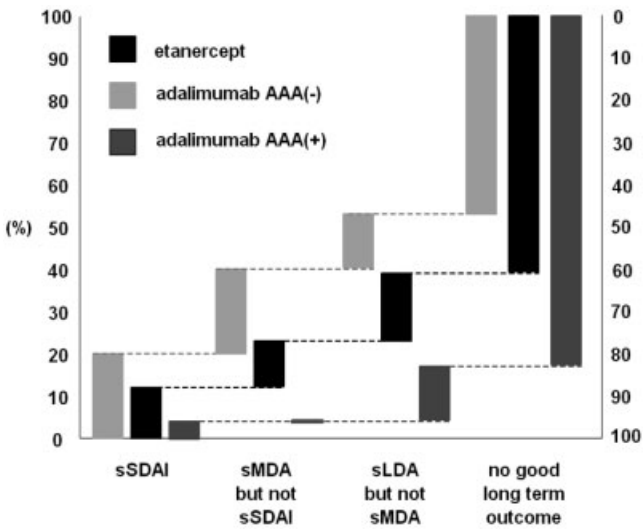

Figure 2. Non-overlapping outcome rates in the adalimumab cohort subclassified according to immunogenicity and the etanercept cohort. AAA($-$) = anti-adalimumab antibody negative; AAA($+$) = anti-adalimumab antibody positive (see Figure 1 for other definitions).

adalimumab-treated patients in the odds of achieving a better clinical outcome). However, the presence or absence of anti-adalimumab antibodies in adalimumab-treated patients significantly affected response compared with etanercept-treated patients. Adalimumab-treated patients who were negative for anti-adalimumab antibodies had better treatment responses, whereas those who were positive for anti-adalimumab antibodies

Table 2. Rates of response in the etanercept-treated RA patients and in the adalimumab-treated RA patients who did and those who did not develop anti-adalimumab antibodies*

Outcome	Etanercept group (n = 203)†	AAA− adalimumab group (n = 150)	AAA+ adalimumab group (n = 54)
No sustained response	61	47	83
sLDA but not sMDA	16	13	13
sMDA but not sSDAI	11	20	0
sSDAI	12	20	4

* The overall difference in non-overlapping response rates for the different outcome categories was significant ($P < 0.0001$). Values are the percent. RA = rheumatoid arthritis; sLDA = sustained low disease activity; sMDA = sustained minimal disease activity; sSDAI = sustained American College of Rheumatology/European League Against Rheumatism remission based on the Simplified Disease Activity Index.
† $P = 0.006$ and $P = 0.008$, respectively, versus the adalimumab-treated patients who were negative and those who were positive for anti-adalimumab antibody (AAA).

Table 3. Odds ratios for achieving better clinical outcome*

	Crude OR (95% CI)	P	Adjusted (95% CI)	P
Etanercept vs. adalimumab†	0.79 (0.54–1.15)	0.217	0.81 (0.54–1.21)	0.336
Etanercept vs. adalimumab AAA−‡	0.53 (0.35–0.79)	0.002	0.55 (0.37–0.83)	0.004
Etanercept vs. adalimumab AAA+‡	3.32 (1.53–7.21)	0.002	2.62 (1.19–5.75)	0.017

* OR = odds ratio; 95% CI = 95% confidence interval; AAA = anti-adalimumab antibody.
† Adjusted for erythrocyte sedimentation rate, C-reactive protein level, Simplified Disease Activity Index, and methotrexate dosage.
‡ Adjusted for methotrexate dosage.

had worse responses, compared with etanercept-treated patients.

DISCUSSION

In this cohort study of anti-TNF–naive RA patients, the overall efficacy of etanercept and adalimumab appeared similar. During a followup of 3 years, almost half of the patients experienced a period of at least low disease activity that lasted at least 1 year, and 12–16% experienced sustained remission according to the new, strict ACR/EULAR criteria. The previously documented immunogenicity (6) had a major impact on long-term clinical outcome. Adalimumab-treated patients who developed anti-adalimumab antibodies had far less favorable treatment outcomes when compared to etanercept-treated patients, with favorable outcomes mostly limited to sustained low disease activity. The proportion of patients with periods of sustained remission or minimal disease activity was higher in the group of adalimumab-treated patients without anti-adalimumab antibodies compared to the etanercept-treated group. These findings were based on non-overlapping response rates and persisted after adjustment for a broad-range of potential confounders.

The stringent ACR/EULAR remission criteria were met in only a small proportion of this population of patients who had received no anti-TNF treatment prior to the study. This indicates that there is a large window of opportunity to increase the efficacy of these costly biologic agents. The pharmacokinetics and binding profiles of adalimumab and etanercept are different (17). The half-life of adalimumab is longer than that of etanercept, due to binding of adalimumab to the neonatal Fc receptor, which initiates "recycling" of the adalimumab molecule (17,18), resulting in higher bioavailability of adalimumab compared to etanercept. However, the formation of anti-adalimumab antibodies is a significant issue: these antibodies have the potential to reduce the efficacy of adalimumab (6,19,20), whereas etanercept

does not appear to generate neutralizing antibodies (9). In future efforts to develop new TNF inhibitors and other biologic agents with better efficacy, these pharmacologic attributes should be taken into account.

In order to increase rates of response to treatment, the search for predictors of response is important. Recently it was shown that higher serum etanercept levels correlated with EULAR response (9). In that study, female sex, high body mass index, and concomitant treatment with low-dose methotrexate were associated with lower etanercept levels and, as a consequence, lower response to etanercept (9). With regard to anti-adalimumab antibodies, we previously showed in this cohort that the risk of developing these antibodies was increased among patients who had longstanding severe disease and those who did not receive concomitant treatment with DMARDs, including low-dose methotrexate (6). These findings may become important in the context of personalized medicine and expediency, i.e., targeting costly drugs to patients who are most likely to benefit from the treatment.

A limitation of this study is the fact that the cohorts were not designed to directly compare efficacy between adalimumab and etanercept. Moreover, despite the adjustment for known confounders, we were not able to exclude confounding by unmeasured factors, for instance radiologic damage and disability related to this damage. Strengths of the study include the source of the data: 2 large, well-defined, single-center cohorts with identical study design and concurrent enrollment of anti-TNF–naive patients, representing daily practice.

In conclusion, the overall efficacy of adalimumab and etanercept in RA patients who have previously not received anti-TNF therapy is similar. Adalimumab appears to be more effective in patients who do not develop antibodies to the drug but less effective in patients who do. These data suggest that, instead of just taking clinical parameters into account, it is necessary to identify pharmacokinetic attributes of the drug,

in order to better achieve a personalized medicine approach in the use of these costly therapies. Identification of patients who are at high risk for the development of anti-adalimumab antibodies and investigation of ways to prevent or reduce the effects of immunogenicity are needed in order to optimize treatment.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Krieckaert 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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Analysis and interpretation of data. Krieckaert, Jamnitski, Nurmohamed, Kostense, Boers, Wolbink.

ROLE OF THE STUDY SPONSOR

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