Effectiveness of a Third Tumor Necrosis Factor-α-blocking Agent Compared with Rituximab After Failure of 2 TNF-blocking Agents in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To compare the effectiveness of a third tumor necrosis factor-α (TNF-α)-blocking agent with rituximab after failure of 2 TNF-blocking agents in patients with rheumatoid arthritis (RA) in daily clinical practice.

Methods. Patients receiving a third TNF-blocking agent or rituximab after failure of 2 TNF-blocking agents were selected from a Dutch biologic registry. The primary outcome was the results from the Disease Activity Score of 28 joints (DAS28) over the first 12 months after start of the third biologic using mixed-model analyses. Secondary outcomes included the course of the Health Assessment Questionnaire (HAQ) and the separate components of the DAS28 over the first 12 months and the change from baseline in DAS28 and HAQ at 3 and 6 months.

Results. The overall course of the DAS28 over the first 12 months was significantly better for rituximab ($p = 0.0044$), as also observed for the HAQ, although the latter results were not statistically significant ($p = 0.0537$). The erythrocyte sedimentation rates, C-reactive protein, and swollen joint counts showed a better course for rituximab ($p = 0.0008$, $p = 0.0287$, $p = 0.0547$, respectively), but not the tender joint counts or visual analog scale for general health. DAS28 decreased significantly in both groups at 3 and 6 months ($p \leq 0.024$), but the change in HAQ was significant for rituximab only at 3 months ($p = 0.009$).

Conclusion. During the first 12 months of therapy, a larger improvement in disease activity and a trend toward a larger decrease in functional disability was observed in patients receiving rituximab. Switching to a biologic with another mechanism of action might be more effective after failure of 2 TNF-blocking agents in RA. (J Rheumatol First Release Sept 1 2011; doi:10.3899/jrheum.101324)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR-α RITUXIMAB EFFECT

Tumor necrosis factor-α (TNF-α)-blocking therapy has been shown to be efficacious in the treatment of rheumatoid arthritis (RA), with response rates of about 70% in the active treatment group, as shown in large, randomized, clinical trials[1,2,3]. However, some patients may fail this therapy due to lack of effect or adverse events. Switching to another TNF-blocking agent can be beneficial after failure of a first TNF-blocking agent[4,5,6,7,8], as applied in daily clinical practice. However, a second TNF-blocking agent is not effective in all patients. After failure of a second TNF-blocking agent, 2 treatment options remain: switch to a third TNF-blocking agent or switch to a biologic with another

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mechanism of action, for instance, B cell-depleting (rituximab) or costimulation-blocking therapies (abatacept). Evidence to support superiority of either option is lacking, as no randomized head-to-head comparison of these 2 strategies has been conducted to date.

Recent publications suggest that switching to B cell-depleting therapy with rituximab might be more beneficial than switching to another TNF-blocking agent after failure of at least 1 TNF-blocking agent, especially after failure of previous TNF-blocking therapy due to ineffectiveness[9,10]. However, the followup times of these studies were short and observations after discontinuation of therapy or retreatment with rituximab were censored in the analyses.

Therefore the decision to switch to another biologic or to start a third TNF-blocking agent remains at the discretion of the treating physician and is not guided by evidence. We investigated which treatment strategy is most effective in daily clinical practice after failure of 2 TNF-blocking agents. Since data regarding abatacept were limited in our study population (available in The Netherlands in daily clinical practice from October 2007), our objective was to compare the effectiveness of rituximab with the effectiveness of a third TNF-blocking agent after failure of 2 TNF-blocking agents in daily clinical practice.

MATERIALS AND METHODS

Patients. RA patients with failure of 2 TNF-blocking agents who received either a third TNF-blocking agent or rituximab with a followup of at least 12 months were selected from the Dutch RhEumatoid Arthritis Monitoring (DREAM) register. This register includes RA patients who started treatment with biologics for the first time in daily clinical practice, and began in 1997 in 1 hospital (Radboud University Nijmegen Medical Centre). Since February 2003, the register contains data from 11 hospitals[11].

All patients were at least 18 years of age and fulfilled the 1987 American College of Rheumatology criteria for RA at inclusion[12]. They satisfied the Dutch criteria for reimbursement of TNF-blocking therapy, i.e., moderate to high disease activity [Disease Activity Score of 28 joints (DAS28) ≥ 3.2] and failure of at least 2 disease-modifying antirheumatic drugs (DMARD) including optimal doses of methotrexate (MTX; 25 mg per week, combined with folic acid). In The Netherlands, treatment with rituximab is allowed in patients who had failed at least 1 TNF-blocking agent or if TNF-blocking therapy was contraindicated.

The data collection protocol for the register was submitted to the ethics committee. Since the register contains data from daily clinical practice, the ethics committee determined that no ethical approval according to the Dutch law was required.

Treatment. The choice of treatment and the dosing schemes were at the discretion of the attending rheumatologist. TNF-blocking therapy was in general given following Dutch labeled doses: infliximab 3 mg/kg intravenously (IV) every 8 weeks after a loading dose at Weeks 0, 2, and 6; etanercept either 25 mg biweekly or 50 mg once weekly subcutaneously; or adalimumab 40 mg subcutaneously every other week. Rituximab was given as 2 infusions of 1000 mg with a 2-week interval. Patients received 50 or 100 mg methylprednisolone IV, 2 mg clemastine IV, and 1000 mg oral acetaminophen as premedication to prevent adverse events during the infusions. Patients could receive retreatment with rituximab according to the international consensus statement, which advises retreating patients after at least 24 weeks in case of increasing disease activity after initial clinical response or in responders who have considerable residual disease activity (DAS28 > 3.2)[13].

TNF-blocking therapy or rituximab could be combined with DMARD and/or corticosteroids. Start and stop dates of the TNF-blocking therapy, rituximab, DMARD and corticosteroids, doses, and reasons for changes were recorded. Retreatment with rituximab was recorded. Unlike other biologics, it is difficult to define an exact stop date for rituximab. The patients who started a new DMARD or biological after 3 months of initiation of rituximab therapy and who were not retreated with rituximab were considered patients who discontinued rituximab therapy.

Outcome measures. Baseline characteristics were recorded, including age, sex, disease duration, number of previous DMARD, and rheumatoid factor (RF) status. Patients were assessed at the start of TNF-blocking therapy or rituximab and every 3 months thereafter. Assessments included tender (TJC) and swollen joint counts (SJC), erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels, and the visual analog scale for general health (VASGH). The DAS28 was calculated to evaluate disease activity[14]. If the DAS28 was missing because of a missing value for ESR, the ESR was imputed by linear multivariate regression using the patient's values for TJC, SJC, and VASGH. Response was defined as good and/or moderate using the European League Against Rheumatology (EULAR) response criteria[15]. Functional disability was assessed by the Health Assessment Questionnaire (HAQ)[16,17].

Analyses. Data of the first 12 months after start of the third TNF-blocking agent or rituximab were used. Analyses were on an intention-to-treat (ITT) basis: patients were analyzed in the treatment group in which they first started, irrespective of whether they discontinued or continued this treatment during the first 12 months of followup. Such an ITT was possible because data collection was continued when patients had stopped using their initial therapy.

Baseline characteristics were expressed as mean (± SD) or as median (interquartile range) values as appropriate and compared between the 2 treatment groups using Pearson's chi-square test for categorical data and the unpaired Student t test or the nonparametric Mann-Whitney U test for continuous data. A description was given of the treatments during the first 12 months of followup after start of the third TNF-blocking agent or rituximab. The percentage of patients receiving rituximab who received a retreatment was described. If patients discontinued therapy, the reason for discontinuation was given.

The primary outcome was the course of the DAS28 over the first 12 months of followup. The secondary outcomes were the course of the HAQ and the separate components of the DAS28 (SJC, TJC, VASGH, ESR, and CRP) over the first 12 months of followup. We used a mixed model to accommodate the dependencies caused by repeated measurements. After evaluating several error structures, we found that a compound symmetry error structure gave the best fit. The independent variables in the full model were treatment, followup time, the square of followup time, and the interactions between treatment and followup time, and treatment and the square of followup time. In the restricted model the interaction terms were dropped. Since maximum likelihood was used as the estimation criterion, we used a likelihood ratio test to evaluate whether the full model gave a superior fit, thus indicating that the development over time was different in the 2 treatment conditions.

To check for possible confounding factors, we tested whether known predictors for treatment outcomes were different between the 2 treatment groups, such as sex, age, disease duration, RF status, concomitant DMARD use, and number of previous DMARD. Univariate analyses showed that none of these factors was different between the 2 treatment groups.

Posthoc, the changes from baseline in DAS28, HAQ, and the separate components of the DAS28 at 3 and at 6 months within the groups were analyzed by paired Student t test. The response rates and percentages of patients who achieved a DAS28 score ≤ 3.2 at 3 and 6 months were described. P values < 0.05 were considered significant. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics. In total, 64 patients with RA received a third TNF-blocking agent and 90 received rituximab after failure of 2 TNF-blocking agents prior to July 2010. Table 1 shows the baseline characteristics. Except for a higher ESR value in the patients receiving rituximab (p = 0.049), there were no differences in baseline characteristics between the 2 treatment groups.

In both groups, most patients had failed a monoclonal antibody (infliximab or adalimumab) and a soluble receptor (etanercept): 80% in the rituximab group and 66% in the third TNF-blocking agent group, respectively.

Treatment during the first 12 months of followup. Figure 1 describes the therapies patients received during the first 12 months after start of the third TNF-blocking agent or rituximab. Of the patients receiving a third TNF-blocking agent, 48% (31/64) still received this treatment up to 12 months. On the other hand, 52% (33/64) of the patients had discontinued therapy. The reason for discontinuation was ineffectiveness in 45% (15/33), adverse events in 42% (14/33), and other reasons in 12% (4/33).

In the rituximab group, 88% (79/90) continued therapy up to 12 months. Of these patients, 54% (43/79) received a retreatment with rituximab. The median time to retreatment was 8.3 months (interquartile range 3.3). In 12% (11/90) of the patients, rituximab therapy was discontinued at 12 months. The main reason for discontinuation in this group was ineffectiveness, in 91% (10/11). One patient discontinued because of adverse events.

Effectiveness on disease activity and functional disability. Figure 2A shows the mean DAS28 at baseline and 3, 6, 9, and 12 months. At 6 months, the mean DAS28 was significantly lower in the rituximab patients [3.91 (SD 1.25) vs 4.54 (SD 1.40), p = 0.021]. Longitudinal analyses showed

Table 1. Baseline characteristics.

Characteristic	Third TNF-blocking Agent, n = 64	Rituximab, n = 90	p
Female (%)	46/64 (72)	66/90 (73)	NS
Age, yrs, mean (SD)	53.3 (12.9)	56.6 (12.2)	NS
Disease duration, yrs, median (IQR)	8.9 (9.2)	10.9 (13.7)	NS
Rheumatoid factor-positive (%)	51/64 (80)	69/90 (77)	NS
No. previous DMARD, median (IQR)	4.0 (2.0)	4.0 (2.3)	NS
DAS28, mean (SD)*	5.1 (1.30)	5.32 (1.25)	NS
SJC28, mean (SD)	9.4 (6.5)	8.7 (5.8)	NS
TJC28, mean (SD)	9.0 (7.5)	8.0 (6.3)	NS
ESR, mm/h, median (IQR)	26.0 (29.5)	31.0 (28.5)	0.049
CRP, mg/l, median (IQR)	10.0 (24.5)	16.0 (38.0)	NS
VASGH, mean (SD)	57.5 (26.9)	60.8 (19.1)	NS
HAQ, mean (SD)**	1.51 (0.64)	1.52 (0.78)	NS
First TNF-blocking agent			
Infliximab (%)	31 (48)	38 (42)	NS
Etanercept (%)	9 (14)	32 (36)	0.003
Adalimumab (%)	24 (38)	20 (22)	0.039
Second TNF-blocking agent			
Infliximab (%)	12 (19)	6 (7)	0.021
Etanercept (%)	33 (52)	40 (44)	NS
Adalimumab (%)	19 (29)	44 (49)	0.017
Third TNF-blocking agent			
Infliximab (%)	21 (33)		
Etanercept (%)	22 (34)		
Adalimumab (%)	21 (33)		
Concomitant therapy			
MTX (%)	34/64 (53)	42/86 (49)	NS
Other DMARD (%)	20/64 (31)	19/86 (22)	NS
Oral corticosteroids (%)	24/64 (38)	38/86 (44)	NS

* DAS28, SJC28, TJC28, and ESR were missing in 17% (11/64), CRP was missing in 23% (15/64), and VASGH was missing in 36% (23/64) of patients receiving a third TNF-blocking agent. DAS28, SJC28, TJC28, and ESR were missing in 10% (9/90), CRP was missing in 12% (11/90), and VASGH was missing in 12% (11/90) of patients receiving rituximab. ** Missing in 34% (22/64) of patients receiving a third TNF-blocking agent and in 19% (17/90) of patients receiving rituximab. DMARD: disease-modifying antirheumatic drug; IQR: interquartile range; DAS28: Disease Activity Score on 28 joints; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VASHG: visual analog scale for general health; HAQ: Health Assessment Questionnaire; TNF: tumor necrosis factor; MTX: methotrexate.

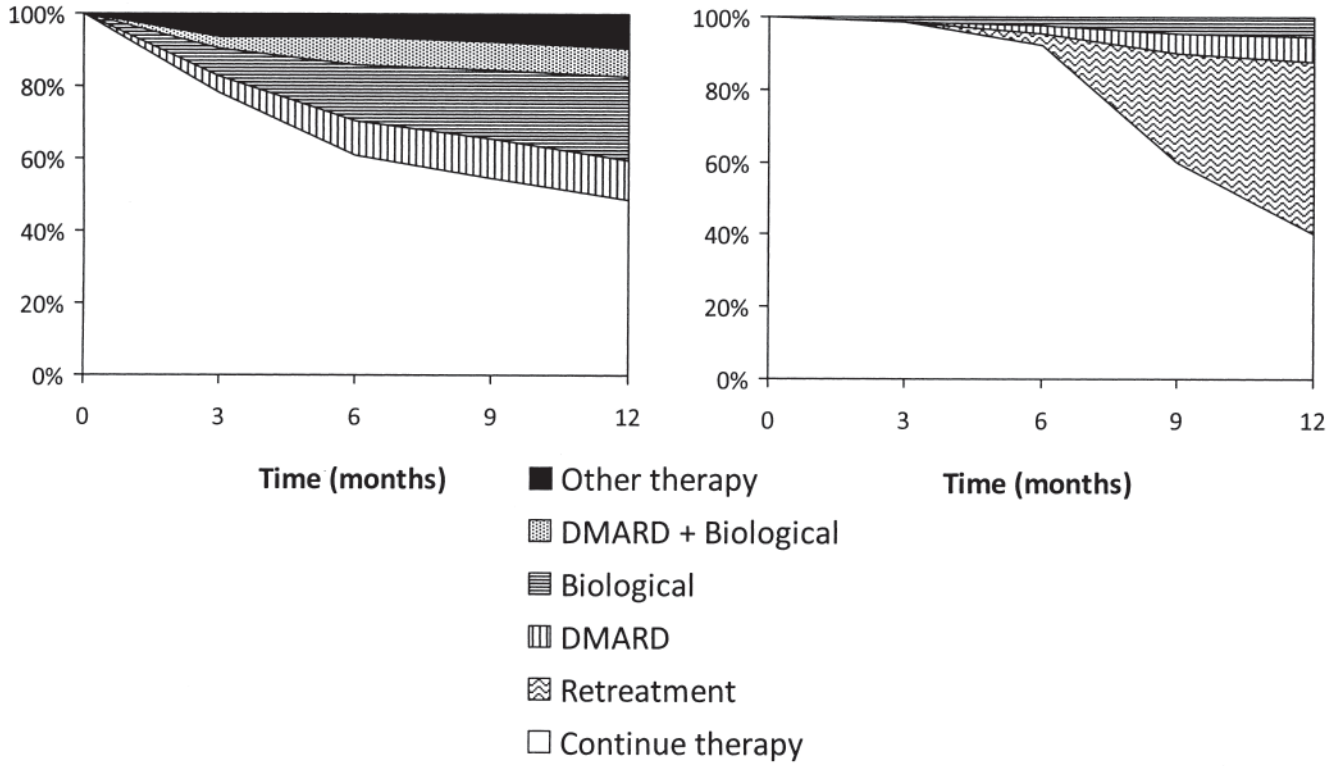

Figure 1. Therapies patients received during the first 12 months after start of the third TNF-blocking agent (A) or rituximab (B) after failure of 2 TNF-blocking agents. Other therapy: no new treatment started, continuation of concomitant DMARD therapy, or information about new treatment is missing. DMARD: disease-modifying antirheumatic drugs.

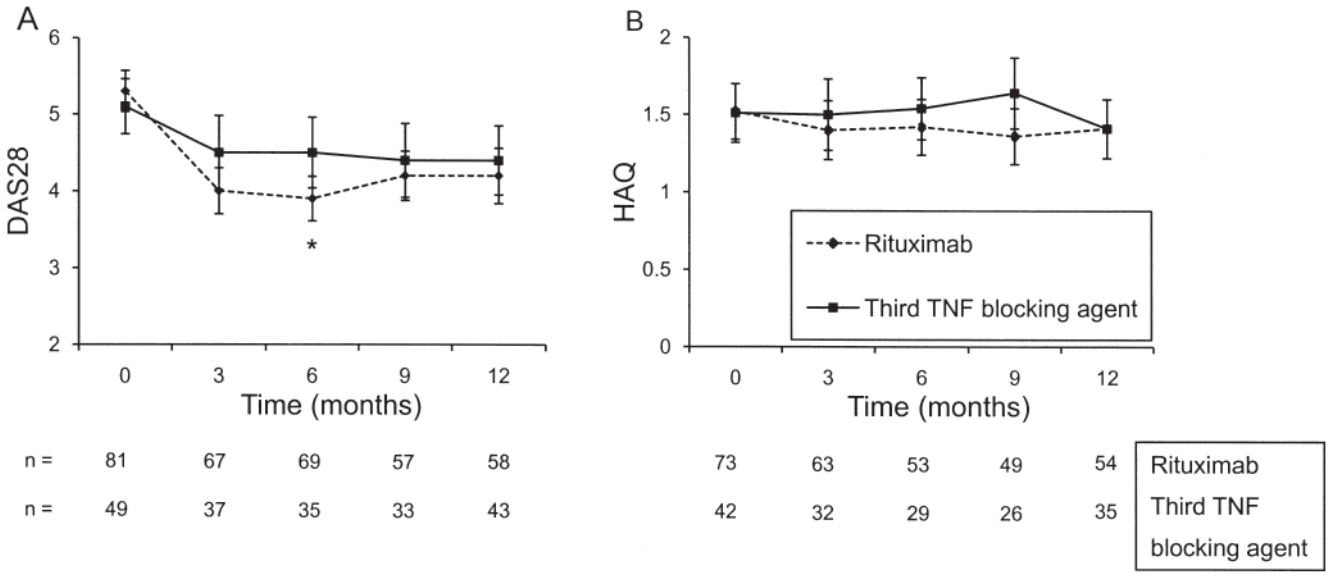

Figure 2. The mean DAS28 scores (A) and the mean HAQ scores (B) over the first 12 months. Bars indicate 95% CI. *Significantly different. DAS28: Disease Activity Score of 28 joints; HAQ: Health Assessment Questionnaire.

that the course of the DAS28 over the first 12 months was significantly better in the rituximab patients (p = 0.0044). In the patients receiving rituximab, the DAS28 showed a slight increase from a mean of 3.9 (SD 1.3) at 6 months to a mean of 4.2 (SD 1.4) at 12 months, which was not significant (p = 0.140).

Figure 2B shows the mean HAQ over the first 12 months of followup. There was a trend to a better course of the HAQ over the first 12 months in the rituximab group, although longitudinal analyses showed a borderline significance (p = 0.0537). The course of the separate components of the DAS28 over time (baseline, 3, 6, 9, 12 mo) showed a pattern similar to the course of the DAS28 over the same period, with an initial decrease up to 6 months and a slight increase thereafter in the rituximab group (data not shown). Longitudinal analyses of the separate components of the DAS28 showed that the course over the first 12 months of followup was better in the rituximab patients for the ESR and CRP (p = 0.0008 and p = 0.0287, respectively). For SJC, the analyses showed a borderline significance (p = 0.0547) in favor of the rituximab group. No difference was observed between the 2 treatment groups for the TJC and VASGH (p = 0.1764, p = 0.348, respectively).

Posthoc analyses showed that the improvement in disease activity was statistically significant at 3 and 6 months in contrast to baseline within both treatment groups. At 3 months this change was –1.01 (SD 1.55, p = 0.001) in the patients receiving a third TNF-blocking agent and –1.35 (SD 1.18, p < 0.0001) in the patients receiving rituximab. At 6 months the change in DAS28 from baseline was –0.58 (SD 1.87, p = 0.024) in the patients receiving a third TNF-blocking agent and –1.39 (SD 1.31, p < 0.0001) in the patients receiving rituximab. The change from baseline in the HAQ was only significant in the rituximab patients at 3 months [–0.23 (SD 0.63), p = 0.009], but not at 6 months [–0.17 (SD 0.58), p = 0.053]. In the patients receiving a third TNF-blocking agent no significant improvement of the HAQ was observed at 3 and at 6 months [–0.17 (SD 0.47), p = 0.070, and 0.09 (SD 0.46), p = 0.309, respectively]. At 3 months and at 6 months, all separate components of the DAS28 improved significantly within the rituximab group (p ≤ 0.007). However, within the patients receiving a third TNF-blocking agent, only the TJC and SJC improved significantly at 3 months (p = 0.045, p = 0.013, respectively) and only the SJC at 6 months (p = 0.034). At 3 months, 60.6% (20/33) of the patients receiving a third TNF-blocking agent and 69.2% (45/65) of the patients receiving rituximab reached a moderate or good EULAR response. At 6 months, these percentages were 48.4% (15/31) and 67.2% (45/67), respectively. The percentage of patients with a DAS28 ≤ 3.2 at 3 and at 6 months in the group receiving a third TNF-blocking agent was 16.2% (6/37) and 18.4% (6/35), respectively. In the rituximab patients, at 3 months 30.4% (21/69) and at 6 months 29.0% (20/69) reached a DAS28 ≤ 3.2.

DISCUSSION

The effectiveness of a third TNF-blocking agent was compared with the effectiveness of rituximab after failure of 2 TNF-blocking agents in patients with RA using observational data from daily clinical practice. In patients receiving rituximab, the overall course of disease activity was better than in the patients receiving a third TNF-blocking agent during the first 12 months. As well, functional disability was lower in the rituximab group, although this did not reach statistical significance. Analyses of the separate components of the DAS28 showed a statistically significant better course of the ESR and CRP in the rituximab patients, a borderline significant better course of the SJC, but no difference in TJC or VASGH between the 2 treatment groups.

The improvement in disease activity in patients receiving a TNF-blocking agent or rituximab was comparable at 6 months after treatment initiation both in our study and a previous study[9]. Notably, we observed a slight increase in disease activity from 6 up to 12 months in the patients receiving rituximab; this was not seen during the 9 months of followup in the study from Finckh, *et al*[9]. In a randomized clinical trial[18], however, a further decline in disease activity was observed when patients were retreated with rituximab during the followup. According to the international consensus statement[13], the Dutch guideline for rituximab therapy in RA advises consideration of retreatment with rituximab after at least 24 weeks in cases of increasing disease activity after initial clinical response, or in responders who have considerable residual disease activity (DAS28 > 3.2). The exact timing of retreatment in our study was at the discretion of the attending rheumatologist. The increase in disease activity may therefore have been caused by a delay among the timing of indication for retreatment, the decision to prescribe a second course by the treating rheumatologist, and the time needed to achieve effect again after retreatment. A previous study also observed some increase in disease activity in the majority of patients before retreatment. Retreatment resulted in a response rate similar to the previous courses in most patients[19]. The followup period of our study was too short to determine the effectiveness of rituximab retreatment. Further research is therefore indicated to investigate the timing of retreatment with rituximab in order to prevent large fluctuations in disease activity in individual patients in daily clinical practice, balanced against potential overdosing with accompanying high costs and possible side effects.

We evaluated only the effectiveness of rituximab therapy compared to a third TNF-blocking agent after failure of 2 TNF-blocking agents. It would also be interesting to compare the effectiveness of rituximab with TNF-blocking therapy earlier in the treatment strategy of RA, for example after failure of 1 TNF-blocking agent or in patients who are naive for TNF-blocking agents. In our cohort, the data of these groups of patients are limited, because in our cohort most

patients to date received rituximab after failure of 2 TNF-blocking agents.

The advantage of the observational design of our study is that the results reflect the effectiveness of TNF-blocking therapy or rituximab in daily clinical practice, including the effects of a decision about when to retreat patients with rituximab. However, an important limitation of using such data is the risk for confounding by indication. Univariate analyses of the baseline characteristics showed only a higher ESR in the patients using rituximab, which might indicate that patients receiving rituximab had more active disease. A rheumatologist might be more inclined to start a biologic with another mechanism of action in such patients after failure of previous TNF-blocking therapy instead of switching to another TNF-blocking agent. However, since the other baseline characteristics did not differ between the 2 treatment groups, we assume that there was no selection by patients of which biologic they received as the third treatment. Therefore, a randomized controlled trial directly comparing the effectiveness of TNF-blocking therapy with the effectiveness of rituximab is indicated to provide a sound answer to this relevant research question. Other limitations of this observational study are the relative low numbers of patients and the high number of missing data. Since the literature shows that analyzing only complete data results in more bias than imputation of missing data[20], we imputed the ESR by means of linear multivariate regression if this value was missing to calculate the DAS28 score. As well, longitudinal analyses using linear mixed models provide more power with small numbers of patients[21] and account for missing data better, since the analyses can handle interindividual differences in time intervals between measurement points. In our study, patients received TNF-blocking agents following Dutch labeled doses. We are aware that in other countries other guidelines for treatment with biologic agents might be present. One could assume that, if higher dosages had been provided, a third TNF-blocking agent would have shown better effectiveness. However, in a previous study the effectiveness of a dose increase of TNF-blocking therapy was limited[22]. Therefore, our results are only generalizable to a situation in which more or less the same guidelines are present as in The Netherlands.

These results from daily clinical practice show a larger improvement in disease activity and a trend toward a larger decrease in functional disability in patients receiving rituximab after failure of 2 TNF-blocking agents during the first 12 months of treatment compared to patients who receive a third TNF-blocking agent. These results might indicate that switching to a biologic with another mechanism of action, such as rituximab, can be more effective than switching to a third TNF-blocking agent after failure of 2 TNF-blocking agents. However, a slight increase in disease activity was observed in the patients receiving rituximab from 6 up to 12 months, which may indicate the need for earlier retreatment. Further research is needed not only to compare the effectiveness of TNF-blocking therapy with the effectiveness of rituximab in a randomized clinical trial, but also to investigate when to retreat patients with RA receiving rituximab in daily clinical practice in order to maintain effectiveness of therapy.

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