

Different Response to Rituximab in Tumor Necrosis Factor Blocker–Naïve Patients With Active Ankylosing Spondylitis and in Patients in Whom Tumor Necrosis Factor Blockers Have Failed

A Twenty-Four–Week Clinical Trial

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Objective. Histologic studies have shown B cell clusters in the subchondral bone marrow of the spine of patients with ankylosing spondylitis (AS). An immunotherapy targeting B cells in AS is therefore of interest. We undertook this study to examine the efficacy and safety of rituximab in patients with AS refractory to nonsteroidal antiinflammatory drugs in whom previous treatment with tumor necrosis factor α (TNF α) blockers either had not been tried or had failed.

Methods. In this phase II clinical trial, 1,000 mg rituximab was administered intravenously at baseline and at week 2 in 20 patients with active AS. Ten of these patients had never received TNF blockers, and treatment with TNF blockers had failed in the other 10 patients. The primary end point was a 20% improve-

ment in disease activity at week 24 according to the criteria of the Assessment of SpondyloArthritis international Society (an ASAS20 response).

Results. Seventy-five percent of the patients were male, 90% were HLA-B27 positive, their mean age was 39.7 years, and their mean disease duration was 16.8 years. Patients had active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 . While there was no clear response at week 24 in the group in whom TNF blockers had failed (30% had achieved an ASAS20 response, 10% had achieved an ASAS40 response, none had achieved partial remission according to the ASAS criteria, and none had achieved 50% improvement on the BASDAI [a BASDAI50 response] beyond an expected placebo response), we observed a good improvement in the TNF blocker–naïve group at week 24 (50% had achieved an ASAS20 response, 40% had achieved an ASAS40 response, 30% had achieved partial remission according to the ASAS criteria, and 50% had achieved a BASDAI50 response).

Conclusion. Although rituximab does not seem to be effective in patients with AS that does not respond to TNF blockers, it had significant efficacy in TNF blocker–naïve patients. Therefore, further controlled trials with B cell–directed therapies should be performed in TNF blocker–naïve AS patients in the future.

Ankylosing spondylitis (AS) is a chronic rheumatic disease predominantly of the axial skeleton (1). Recent recommendations from the Assessment of SpondyloArthritis international Society (ASAS) and the European League Against Rheumatism for the treatment

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of AS state that the management of only 2 groups of drugs are effective for predominant axial manifestations: nonsteroidal antiinflammatory drugs (NSAIDs) and, more recently, tumor necrosis factor α (TNF α) blockers (2). Thus, in contrast to the management of rheumatoid arthritis (RA) and other inflammatory rheumatic diseases, treatment with disease-modifying antirheumatic drugs does not play a role in the management of AS (3–5). Approximately half of AS patients treated with TNF α blockers show a 50% improvement of their disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (6), but 50% do not (7,8). Alternative treatment options are urgently needed, especially for the latter patients who experience no or only a suboptimal response to anti-TNF agents and for AS patients who cannot be treated with TNF α blockers because of contraindications.

Histologic studies (9,10) and magnetic resonance imaging (MRI) investigations (11) suggest that the primary site of inflammation is the cartilage/bone interface. Mononuclear cell infiltrates are mainly found in cartilage and the subchondral bone. In early and active sacroiliitis, T cells and macrophages are dominant in these infiltrates, underlining the relevance of a specific cellular immune response (10). Rather surprisingly, however, dense infiltrations of B cells in the subchondral bone marrow were also found in these patients. The number of B cells in AS was even higher than the number of T cells, in contrast to findings in immunohistologic stainings from control subjects without spinal disease (12,13).

Based on the immunohistologic findings of those studies (12,13) and on the good efficacy observed in RA trials, we conducted an open-label trial in patients with active AS as a proof-of-concept trial with the B cell-directed antibody rituximab. Rituximab targets CD20+ B cells; it was first approved for the treatment of lymphoma (14) and most recently also for the treatment of RA (15).

PATIENTS AND METHODS

Procedures. In this open-label phase II clinical trial, 20 patients with active AS received 1,000 mg rituximab intravenously at baseline and at week 2 together with 100 mg methylprednisolone, similar to a regimen described previously (15). Patients were then followed up every 4 weeks until week 24. The study was approved by an independent ethics committee and was conducted at 2 centers in Germany (Charité Medical University Hospital, Berlin and Centre of Rheumatology, Herne) in accordance with the ethics principles of the Declaration of Helsinki. Rituximab was provided by Roche Pharma AG.

All patients had a diagnosis of AS according to the modified New York criteria (16) and had active disease, defined as a BASDAI score ≥ 4 and a back pain score of ≥ 4 (BASDAI question 2), despite treatment with at least 2 NSAIDs at the maximum tolerated dosage. Concomitant treatment with steroids (≤ 10 mg/day prednisone), methotrexate (MTX), or sulfasalazine was permitted, but patients had to be receiving a stable dosage 4 weeks prior to baseline. If a patient was receiving TNF α -blocking agents, this treatment had to be terminated at least 4 weeks prior to baseline in the case of etanercept and at least 8 weeks prior to baseline in the case of infliximab or adalimumab. TNF α inhibitor failure was defined according to the opinion of the local rheumatologist; however, we excluded patients who discontinued TNF-blocking treatment because of side effects. In order to address the question of whether TNF blocker-naïve patients and patients in whom TNF blocker had failed would respond differently to rituximab treatment, 10 TNF blocker-naïve patients with active AS and 10 patients with active AS in whom TNF blocker had failed were prospectively included in the study. Exclusion criteria included uncontrolled concomitant diseases, abnormal or clinically relevant changes on clinical examinations and laboratory testing, or pregnancy.

Clinical outcome assessments were performed every month, and included the BASDAI, the Bath Ankylosing Spondylitis Functional Index (BASFI) (17), the linear Bath Ankylosing Spondylitis Metrology Index (BASMI) (18), quality of life measurement using the Medical Outcomes Study Short Form 36 health survey (19), the Ankylosing Spondylitis Quality of Life questionnaire (20), and the EuroQol (21), patient's and physician's global assessments of disease activity (0–10 scales), number of swollen joints (64 joints), and an enthesitis score (the Maastricht Ankylosing Spondylitis Enthesitis Score [22]). Laboratory outcome assessments included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level.

The primary end point was 20% improvement in disease activity at week 24 according to the ASAS criteria (an ASAS20 response) (23,24) in the whole group as well as in 2 subgroups. Secondary outcome parameters were 40% improvement according to the ASAS criteria (an ASAS40 response), partial remission according to the ASAS criteria, 20% and 50% improvement on the BASDAI (BASDAI20 and BASDAI50 responses), and mean improvement on the BASDAI and the BASFI and in health-related quality of life.

MRI of the spine using T1-weighted and STIR sequences was performed at screening and at week 24. The extent of inflammation in the spine was then quantified by 2 readers by consensus reading according to the score on the Berlin modification of the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASSpiMRI-a) (25). In addition to routine laboratory tests, levels of CD20+ and CD19+ B cells were analyzed throughout the study.

Statistical analysis. Statistical analysis was performed as an intent-to-treat, last observation carried forward analysis. The nonparametric Wilcoxon signed rank test was used to compare changes between baseline and after-treatment values. *P* values less than 0.05 were considered significant.

Table 1. Baseline characteristics of the total group of patients with ankylosing spondylitis as well as of the 2 subgroups of patients who were treated with rituximab (patients who were TNF blocker naive and patients in whom TNF blockers had failed)*

Parameter	Total group (n = 20)	TNF blocker naive (n = 10)	TNF blocker failed (n = 10)	P, TNF blocker naive vs. TNF blocker failed
Age, years	39.7 ± 10.6	37.2 ± 10.5	42.2 ± 10.6	NS
Male, %	75	80	70	NS
HLA-B27 positive, %	90	100	80	NS
Disease duration, years	16.8 ± 9.5	13.0 ± 8.9	20.5 ± 8.9	NS
BASDAI score, 0–10	6.1 ± 1.3	5.7 ± 1.6	6.5 ± 0.9	0.043
Patient's global assessment of disease activity, 0–10	7.0 ± 2.0	6.3 ± 2.2	7.6 ± 1.6	NS
BASFI score, 0–10	5.4 ± 2.2	4.3 ± 1.9	6.5 ± 1.9	0.011
Physician's global assessment of disease activity, 0–10	6.5 ± 1.0	6.0 ± 0.7	7.0 ± 0.9	0.014
MASES, 0–13	3.7 ± 5.0	2.0 ± 4.0	5.4 ± 5.5	NS
No. of swollen joints, 0–64	2.1 ± 2.4	1.5 ± 2.2	2.6 ± 2.6	NS
Linear BASMI score, 0–10	3.4 ± 2.0	2.5 ± 0.7	4.3 ± 2.4	NS
CRP, mg/liter†	26.3 ± 33.3	24.6 ± 32.8	28.0 ± 35.5	NS
Modified Berlin spine score, 0–69‡	6.11 ± 6.0	6.50 ± 7.3	5.63 ± 4.4	NS
Patients with active inflammatory lesions in spine on MRI, %	94.5	100	87.5	NS
CD20+ cells§	241.7 ± 87.9	277.2 ± 96.4	202.2 ± 60.0	NS

* Except where indicated otherwise, values are the mean ± SD. TNF = tumor necrosis factor; NS = not significant; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = C-reactive protein; MRI = magnetic resonance imaging.

† Normal ≤5 mg/liter.

‡ Score on the Berlin modification of the Ankylosing Spondylitis spine Magnetic Resonance Imaging–activity.

§ B cell marker; normal 166–392/μL.

RESULTS

Baseline characteristics. Of the 20 patients with AS who were enrolled in this study, 10 had never received TNF blockers, and TNF blockers had failed in 10 others. Among those AS patients who had been treated with TNFα blockers before the study, 6 patients had received 1 TNFα blocker, 3 had received 2 TNFα blockers, and 1 had been treated with 3 TNFα blockers. Demographic data for all patients as well as for the 2 subgroups are shown in Table 1. There was no difference at baseline between TNF blocker–naïve patients and patients in whom TNF blockers had failed regarding the parameters assessed in this study, except that patients previously treated with TNFα blockers had slightly higher mean values for the BASDAI and BASFI scores and the physician's global assessment of disease activity.

Primary and secondary end points. At week 24 in both groups of AS patients combined, 40% achieved an ASAS20 response (95% confidence interval [95% CI] 20.9–64.0%), 25% achieved an ASAS40 response (95% CI 10.4–46.7%), 15% achieved partial remission according to the ASAS criteria (95% CI 4.2–36.1%), 40% achieved a BASDAI20 response (95% CI 20.9–64.0%), and 25% achieved a BASDAI50 response (95% CI 10.4–46.7%) (Figure 1). However, response rates were

clearly higher in the 10 TNF blocker–naïve patients, with 50% achieving an ASAS20 response (95% CI 22.3–77.8%), 40% achieving an ASAS40 response (95% CI 15.0–73.3%), 30% achieving partial remission according to the ASAS criteria (95% CI 8.7–61.9%), 60% achieving a BASDAI20 response (95% CI 26.7–85.0%), and 50% achieving a BASDAI50 response (95% CI 22.3–77.8%). As shown in Figures 1 and 2, significantly more TNF blocker–naïve patients achieved a BASDAI50 response than did patients in whom TNF blockers had failed ($P = 0.033$). When we compared the clinical response between TNF blocker–naïve patients ($n = 10$) and patients in whom TNF blockers had failed ($n = 8$) in HLA-B27–positive patients alone, the respective response rates were similar (50% versus 25% for achieving an ASAS20 response, 40% versus 12.5% for achieving an ASAS40 response, 30% versus 0% for achieving partial remission according to the ASAS criteria, 60% versus 25% for achieving a BASDAI20 response, and 50% versus 0% for achieving a BASDAI50 response).

A clinical response to rituximab occurred as early as 4–8 weeks after the first rituximab infusion, but the highest response was achieved at week 16 (Figures 2 and 3). The best response in terms of a decrease in the CRP level was also seen at week 16 (Figure 4).

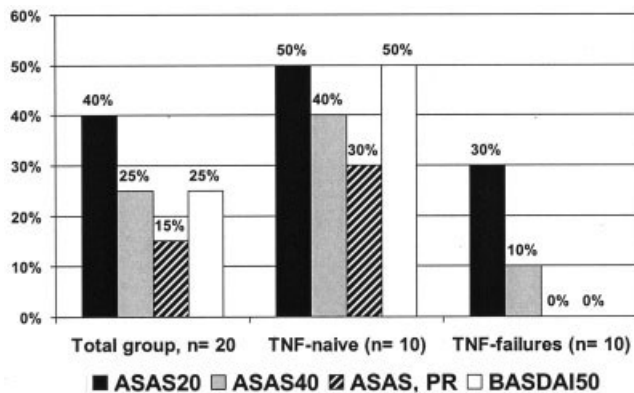


Figure 1. Percentages of patients with active ankylosing spondylitis achieving 20% improvement in disease activity according to the criteria of the Assessment of SpondyloArthritis international Society (an ASAS20 response), an ASAS40 response, partial remission (PR) according to the ASAS criteria, and 50% improvement on the Bath Ankylosing Spondylitis Disease Activity Index (a BASDAI50 response) 24 weeks after treatment with rituximab. Data are shown for all patients combined and for the subgroups of tumor necrosis factor (TNF) blocker-naïve patients and patients in whom TNF blockers had failed.

The mean BASDAI score changed significantly by 1.4 points in both groups combined, from 6.1 at screening to 4.7 at week 24 ($P = 0.004$). The change was even more pronounced in the TNF blocker-naïve patients, with a 2-point change in the mean BASDAI score, from 5.7 to 3.7 ($P = 0.047$) (Figure 3). Statistically

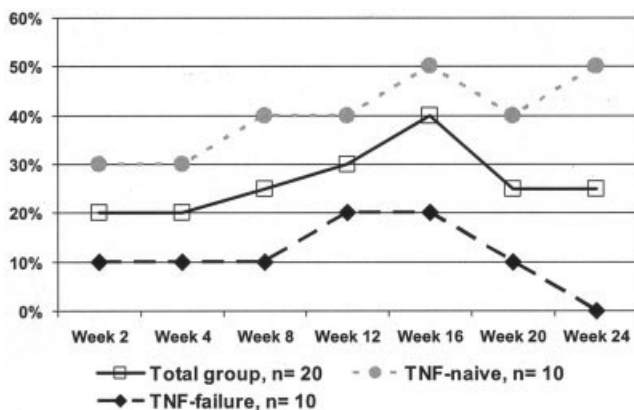


Figure 2. Percentages of patients with active ankylosing spondylitis in all 3 groups (all patients combined as well as the subgroups of TNF blocker-naïve patients and patients in whom TNF blockers had failed) achieving a BASDAI50 response at weeks 2 through 24 after treatment with rituximab (1,000 mg at baseline and at week 2). At week 24, significantly more TNF blocker-naïve patients achieved a BASDAI50 response than did patients in whom TNF blockers had failed ($P = 0.033$). See Figure 1 for definitions.

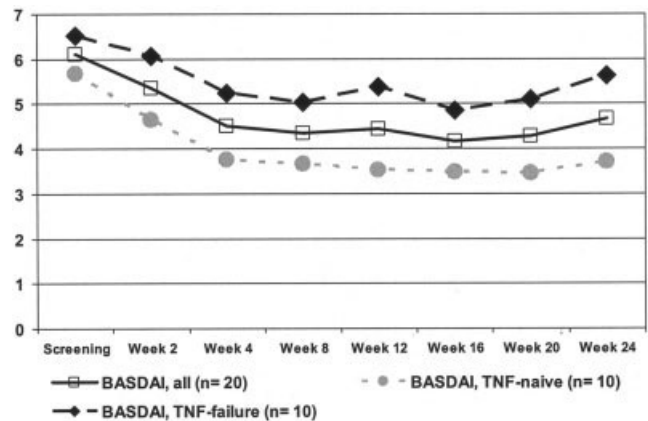


Figure 3. Mean BASDAI score over the period of 24 weeks in all 3 groups (all patients combined as well as the subgroups of TNF blocker-naïve patients and patients in whom TNF blockers had failed). See Figure 1 for definitions.

significant changes were also found between screening and week 24 for patient's global assessment of disease activity, BASDAI question 2 (dealing with back pain), global pain, BASFI score, physician's global assessment of disease activity, and the BASMI score in both groups combined; for BASDAI question 2, global pain, and CRP level in TNF blocker-naïve patients; but only for BASDAI question 2 in patients in whom TNF blockers had failed (Table 2 and data not shown). Treatment with rituximab resulted in a nearly complete depletion of peripheral CD19+ B lymphocytes (data not shown) and CD20+ B lymphocytes (decrease from $\sim 240/\mu\text{l}$ at screening to $<10/\mu\text{l}$ at week 12) within the first weeks

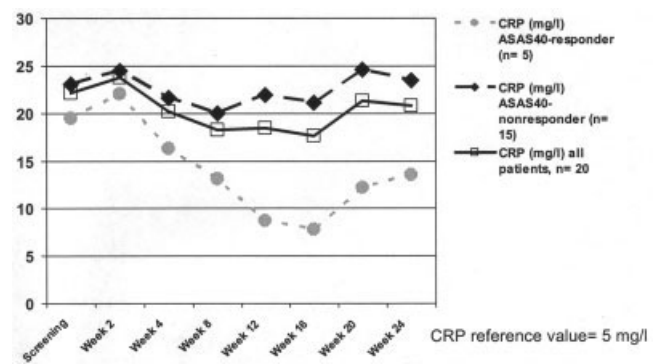


Figure 4. Mean C-reactive protein (CRP) level in patients with active ankylosing spondylitis achieving 40% improvement in disease activity according to the criteria of the Assessment of SpondyloArthritis international Society (ASAS40 responders) compared with that in ASAS40 nonresponders and in the total group of patients treated with rituximab. CRP reference value = 5 mg/l.

Table 2. Summary of secondary outcome measures at week 24 compared with screening in the total group of patients with ankylosing spondylitis as well as in the 2 subgroups of patients who were treated with rituximab (patients who were TNF blocker naïve and patients in whom TNF blockers had failed)*

Secondary outcome parameter	Week 24 value, mean $\pm$ SD			Change from screening to week 24, mean $\pm$ SD		
	Total group (n = 20)	TNF blocker naïve (n = 10)	TNF blocker failed (n = 10)	Total group (n = 20)	TNF blocker naïve (n = 10)	TNF blocker failed (n = 10)
BASDAI score, 0–10	4.7 $\pm$ 1.9†	3.7 $\pm$ 2.0†	5.6 $\pm$ 1.2†	–1.4 $\pm$ 1.8†	–2.0 $\pm$ 2.2†	–0.9 $\pm$ 1.3†
Patient's global assessment of disease activity, 0–10	5.3 $\pm$ 2.6†	4.1 $\pm$ 2.7	6.5 $\pm$ 1.9	–1.7 $\pm$ 2.6†	–2.2 $\pm$ 3.2	–1.1 $\pm$ 1.7
BASFI score, 0–10	4.5 $\pm$ 2.4†	3.0 $\pm$ 2.0	6.0 $\pm$ 1.8	–0.9 $\pm$ 1.9†	–1.3 $\pm$ 2.2	–0.5 $\pm$ 1.6
Linear BASMI score, 0–10	3.0 $\pm$ 1.9†	2.1 $\pm$ 0.6	4.0 $\pm$ 2.3	–0.4 $\pm$ 0.7†	–0.4 $\pm$ 0.6	–0.3 $\pm$ 0.7
MASES, 0–13	1.3 $\pm$ 3.0	0.3 $\pm$ 0.8	2.5 $\pm$ 4.3	–2.4 $\pm$ 3.4	–1.7 $\pm$ 4.0	–2.9 $\pm$ 3.0
Physician's global assessment of disease activity, 0–10	4.4 $\pm$ 2.6†	3.4 $\pm$ 2.9	5.8 $\pm$ 1.6	–2.1 $\pm$ 2.5†	–2.6 $\pm$ 2.6	–1.2 $\pm$ 2.4
No. of swollen joints, 0–64	0.9 $\pm$ 2.8	0.1 $\pm$ 0.4	1.7 $\pm$ 4.1	–1.2 $\pm$ 3.0	–1.4 $\pm$ 1.9	–0.9 $\pm$ 4.2
ASQoL questionnaire score, 0–18	6.9 $\pm$ 3.5	5.5 $\pm$ 4.1	8.7 $\pm$ 1.5	–3.4 $\pm$ 4.5	–3.3 $\pm$ 3.4	–3.1 $\pm$ 5.2
CRP, mg/liter‡	24.2 $\pm$ 28.3	19.1 $\pm$ 26.7†	29.4 $\pm$ 30.3	–2.1 $\pm$ 14.1	–5.5 $\pm$ 7.2†	–1.4 $\pm$ 18.5
Modified Berlin spine score, 0–69§	6.3 $\pm$ 6.8	8.3 $\pm$ 8.6	4.0 $\pm$ 3.2	+0.2 $\pm$ 4.1	+1.8 $\pm$ 2.0	–1.6 $\pm$ 5.4
CD20+ cells¶	17.5 $\pm$ 43.1†	12.6 $\pm$ 20.0†	21.8 $\pm$ 57.6†	–224.2 $\pm$ 95.3†	–264.6 $\pm$ 104.1†	–180.4 $\pm$ 68.0†

* ASQoL = Ankylosing Spondylitis Quality of Life (see Table 1 for other definitions).

† $P < 0.05$ versus screening.

‡ Normal ≤ 5 mg/liter.

§ Score on the Berlin modification of the Ankylosing Spondylitis spine Magnetic Resonance Imaging–activity.

¶ B cell marker; normal 166–392/ μ l.

after the first rituximab infusion, with a small increase observed until week 24 (Table 2).

The mean CRP and ESR values in the total group did not change significantly (Table 2). However, in TNF blocker-naïve patients the CRP concentrations decreased significantly by 5.5 mg/liter, from 24.6 mg/liter at screening to 19.1 mg/liter at week 24 ($P = 0.017$). The decrease in CRP concentration was even more pronounced in the 5 ASAS40 responders (Figure 4).

As far as active inflammatory changes on MRI were analyzed, there was no change in the mean score on the Berlin modification of the ASSpiMRI-a (Table 2). The score also did not improve in the 3 patients who achieved partial remission according to the ASAS criteria (scores of 1 before versus 4 after, 26 before versus 27 after, and 7 before versus 6 after) or in the 3 ASAS40 responders in whom the CRP concentration decreased significantly (scores of 10 before versus 9 after, 4 before versus 2 after, and 26 before versus 27 after).

Dropouts. Eighteen of 20 patients (90%) continued in the study through week 24. One young male TNF blocker-naïve patient withdrew after 8 weeks for personal reasons (noncompliance; lost to followup), and 1 female TNF blocker-naïve patient withdrew at week 20 because of inefficacy.

Safety. During the 24-week phase of the study, we noted no new side effects in addition to those already

observed in other studies (15,26,27). A total of 90 adverse events (AEs) occurred until week 24. Infections of the upper respiratory tract ($n = 13$) and infusion reactions ($n = 7$) were the most commonly reported AEs. Of note, no rituximab infusion had to be discontinued. There were 5 serious AEs. One serious AE (surgical treatment of hemorrhoids), which was definitely not drug related, occurred before baseline. The other serious AEs were an ulnar fracture, a case of nephrolithiasis, a skin abscess after colonoscopy, and an episode of gastrointestinal bleeding. None of these were considered to be related to the study drug.

DISCUSSION

This is the first study assessing the efficacy of rituximab in AS. We could show that AS patients who have not previously been treated with TNF α -blocking agents have a good response to rituximab treatment. An ASAS40 response was achieved by 40% of these TNF blocker-naïve patients, a BASDAI50 response was achieved by 50%, and partial remission according to the ASAS criteria was achieved by 30%. This comes close to the clinical response rate of patients treated with TNF α blockers (28–30).

The response to rituximab already started 4–8 weeks after the first rituximab infusion and was sus-

tained during treatment up to 24 weeks. This speed of response is comparable with the efficacy in RA (e.g., results from the Randomized Evaluation of Long-Term Efficacy of Rituximab in RA [REFLEX] Trial showed that the clinical benefit of rituximab had already started 4 weeks after the first infusion, with improvements in the Disease Activity Score in 28 joints [31] of -1.6 after 4 weeks and -1.8 after 12 weeks [15]). While the effect seen at week 4 might have been influenced by the concomitant administration of prednisolone, which was given to prevent allergic reactions, it is unlikely that a possible glucocorticoid effect lasted until week 16 (32,33). Currently, there is no evidence that glucocorticoids are effective at all in the treatment of AS (2). In a few small uncontrolled trials with pulse methylprednisolone therapy, it could be demonstrated that the effect of 1 pulse of 1,000 mg does not last longer than 4 weeks (34,35). A maximal response to treatment was observed at week 16, similar to the response to rituximab in RA (15).

Not only did rituximab treatment result in a good clinical response, but CRP levels also decreased significantly (Figure 4), especially in the TNF blocker-naïve patients. However, active inflammation of the spine as shown on MRI did not change between week 0 and week 24. The reason for this is not clear, but week 24 might not have been the best time point for this observation, since the highest clinical efficacy was seen 8 weeks earlier. Future studies with rituximab or other B cell-directed therapies should therefore include MRI investigations at earlier time points.

So far, there are only a few case reports on the efficacy of rituximab in AS, and these describe conflicting results (36–41). Interestingly, those AS patients in whom TNF α blockers failed showed no response to rituximab treatment; these included 1 young female patient who had previously been treated with 3 TNF α blockers (39), 1 male patient who was previously treated with etanercept (41), 1 female patient who had only a partial response (40), and 2 more patients from a French registry (38). In contrast, 3 TNF blocker-naïve AS patients were described for whom TNF α blockers were contraindicated; all responded well to rituximab treatment (36–38). Thus, similar to our patients, patients in whom TNF blockers had failed did not have a good response, while TNF blocker-naïve patients responded better to rituximab treatment.

We also saw some response in the group of patients in whom TNF blockers had failed. However, this response was not higher than that observed in the placebo groups in placebo-controlled trials (29,30,42).

Importantly, the small response seen in this group was clearly lower than the reported improvement in AS patients in whom TNF blockers had failed and who were switched to a second TNF blocker. An ASAS40 response rate of up to 47% for those patients was recently reported from an open-label trial (43). This is in contrast to failures of TNF blockers in RA patients who showed a good response to rituximab (15). Thus, rituximab does not seem to be an option for patients with AS that does not respond to a TNF blocker.

We have previously performed several open-label trials in which various drugs were administered subcutaneously, such as anakinra (4) and MTX (5). No improvement in disease activity was seen in those studies, suggesting that the response rate seen in the present trial in the TNF blocker-naïve group might be real. Obviously, these good results in TNF blocker-naïve patients have to be confirmed in a controlled trial, either against placebo or even against a TNF blocker. These results also raise a question about the possible mechanism of a B cell-directed therapy in AS. At the moment, there is no evidence that (auto)antibodies play any role in the pathogenesis of AS. B cells are also potent antigen-presenting cells, and an inhibition of this function might be an alternative explanation. In any case, our results suggest that TNF blockers and anti-B cell therapies suppress a similar pathway. This interpretation, which is also supported by the lack of efficacy in patients who did not previously experience a response to TNF blockers, might differ from that for RA, for which it had been speculated that different drugs might be effective for different pathways, possibly resulting in a “tailored” treatment choice in the future (44). The outcome of the present study also confirms findings of earlier immunohistologic investigations by our group (12), that B cells might have a role, ill defined until now, in the immune response in AS.

Based on our results, rituximab treatment might currently be considered in AS patients with contraindications for TNF blockers such as previous lymphoma, demyelinating diseases (45), lupus-like syndromes (46–48), or others (49–53) until further results from controlled trials become available.

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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. Sieper 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.

Study conception and design. Song, Rudwaleit, Listing, Appel, Sieper. **Acquisition of data.** Song, Heldmann, Braun, Sieper.

Analysis and interpretation of data. Song, Rudwaleit, Listing, Appel, Sieper.

ROLE OF THE STUDY SPONSOR

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