

Rituximab Therapy in Rheumatoid Arthritis in Daily Practice

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ABSTRACT. Objective. Rituximab has been shown to be effective in refractory rheumatoid arthritis (RA) in randomized controlled trials, allowing approval by health agencies. Our aim was to assess in routine care the effects of rituximab in patients with RA who had experienced an inadequate response to anti-tumor necrosis factor- α (TNF- α) agents or had a contraindication to these drugs.

Methods. An observational retrospective study was conducted. Rituximab (1000 mg intravenous infusion on Days 1 and 15) was administered with concomitant methotrexate therapy. Responses defined according to the European League Against Rheumatism (EULAR criteria) were assessed at Week 24.

Results. Fifty patients were included: 30 had inadequate response to anti-TNF- α and 20 had contraindication to anti-TNF- α drugs. EULAR response was observed in 82%, good response in 36% (including remission in 12%), moderate response in 46%, and no response in 18%. One infusion-related reaction and 2 pulmonary infections occurred. Eleven of the 50 patients (22%) experienced flare and received retreatment with rituximab at 6 months. Thirty additional patients had flare after 6 months and the median delay for retreatment among the 41 responders was 9 (range 6–24) months. No difference regarding efficacy or tolerance of rituximab was observed according to previous inadequate response or contraindication to anti-TNF.

Conclusion. A single cycle of rituximab, in combination with continued methotrexate, provided significant improvement in disease activity at Week 24, with good tolerance, in patients with severe and active RA despite anti-TNF- α agents and/or with contraindication to these drugs, in this daily practice study. (First Release Nov 15 2007; J Rheumatol 2008;35:31–4)

Key Indexing Terms:

RITUXIMAB

RHEUMATOID ARTHRITIS

OPEN-LABEL TRIAL

Rheumatoid arthritis (RA) is a chronic disease that leads to inflammation and joint damage. Current therapies target the inflammatory consequences of autoimmune activation with the use of disease modifying antirheumatic drugs (DMARD) such as methotrexate (MTX) and biologic DMARD. Despite the efficacy of agents such as tumor necrosis factor- α (TNF- α) inhibitors, 30% of patients seem to have no response or no sustained response¹. While the exact pathogenesis of RA has not been fully established, evidence suggests the importance of B lymphocytes in RA; these cells are present in the inflamed synovium and contribute to the inflammatory process and joint destruction by processing autoantigen and presenting it to T lymphocytes, by autoantibody generation, and by cytokine secretion².

Rituximab is a chimeric monoclonal antibody that selectively binds CD20 on mature B cells; it has recently been shown to be effective in suppressing disease activity in RA. Randomized trials have demonstrated efficacy both in MTX-resistant³ and in anti-TNF therapy-resistant patients^{4,5}. However, it is recognized that the value of these trials in predicting therapeutic effectiveness in “real-world” patients is limited⁶. Hence data from daily practice experience are important to confirm the results from trials. We describe our experience of treating patients with RA with rituximab where they had experienced an inadequate response to treatment with anti-TNF- α agents or had a contraindication to these drugs.

MATERIALS AND METHODS

This was a retrospective observational study performed in 3 tertiary rheumatology units between 2004 and 2006. Patients with RA fulfilling the 1987 American College of Rheumatology criteria⁷ who were resistant to anti-TNF agents (treated with any agent for at least 3 months) or who had contraindication to these drugs (history of recurrent infection or tuberculosis, personal or family history of multiple sclerosis, heart failure, malignancy) and had persistent disease activity despite DMARD were considered for treatment with rituximab. Subjects eligible for enrolment were adult patients who had active disease defined by Disease Activity Score (DAS28) > 3.2. Concomitant therapy consisted of MTX and low-dose prednisone (5–10 mg/day) throughout the study period. Rituximab was administered as a 1000-mg intravenous infusion on Days 1 and 15 with 100 mg methylprednisolone before each infusion

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Accepted for publication September 24, 2007.

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according to previous recommendations⁸. DAS28 scores were analyzed at baseline and 6 months posttreatment: European League Against Rheumatism (EULAR) response at Week 24 was analyzed as the main outcome measure. Moderate response was defined as improvement of DAS28 value > 0.6 with DAS28 at endpoint < 5.1, or improvement of DAS28 value > 1.2 with DAS28 at endpoint > 5.1. Good response was defined as improvement of DAS28 value > 1.2 with DAS28 at endpoint < 3.2. Remission was defined by DAS28 < 2.6⁹. Patients were retreated with a second cycle of rituximab if they had responded to the earlier one but experienced flare with a DAS28 score > 3.2.

Results are provided as medians and ranges. Differences in clinical scores were determined using the chi-square method for comparison of proportions and Wilcoxon tests for paired nonparametric data (comparison of baseline and followup data), and a *p* value < 0.05 was considered significant.

RESULTS

Fifty patients with active RA received rituximab: 43 (86%) were women, of mean age 58 ± 10 years and with mean disease duration at inclusion of 15 ± 9 years. Rheumatoid factor (RF) was positive in 45/50 patients and anti-cyclic citrullinated protein (CCP2) antibodies in 47/50 as determined by ELISA methods. The patients had highly active disease, as shown by the high median values of DAS scores and C-reactive protein values at baseline (Table 1). Thirty patients had had an inadequate response to anti-TNF, of whom 10 had been treated with all 3 available anti-TNF-α drugs (etanercept, infliximab, and adalimumab) and 14 with 2 drugs. Twenty patients (40%) were considered to have a contraindication to anti-TNF-α drugs [history of recurrent infections or tuberculosis (*n* = 11), personal or family history of multiple sclerosis (*n* = 3), previous lymphoma (*n* = 3), heart failure (*n* = 2), or vasculitis occurring during etanercept treatment (*n* = 1)]. All of them had previously been treated with MTX; the mean number of previous DMARD not including MTX was 3.5 ± 1.4. There were no differences in baseline characteristics in the subgroup of RA patients with contraindication to anti-TNF-α compared to the subgroup with previous failure to anti-TNF-α drugs: mean age 57 ± 10 years versus 57 ± 6 years, number of men 4/20 versus 3/30, disease duration 14 ± 12 years versus 11 ± 10 years, 18/20 RF-positive versus 27/30 RF-positive, and 20/20 anti-CCP-positive versus 27/30 anti-

CCP-positive. Concomitant therapy consisted of MTX (12.5–20 mg/wk) and low-dose prednisone (5–10 mg/day).

The response to first cycle of rituximab is shown in Table 1 and Table 2 for the whole cohort and separately for the 2 different subgroups, according to inadequate response versus contraindication to anti-TNF. There was a significant decrease in DAS28 score: median reduction of 1.8 (–2.1; +4.9, *p* < 0.0001); individual changes are shown in Figure 1. EULAR response was seen in 82% of patients: a moderate response in 46%, good response in 36% (including 12% in remission); no response was seen in 18%. However, taking into account the patients who required retreatment at 6 months together with those with lack of efficacy, 20/50 (40%) could be considered nonresponders. There was no statistically significant difference for the responses between the groups of patients with contraindication to anti-TNF-α drugs versus the group refractory to anti-TNF drugs (Table 1 and Table 2). In addition, there was no difference between patients positive or negative for RF. One infusion-related reaction and 2 pulmonary infections occurred; these resolved without sequelae. Patients with infection did not have hypogammaglobulinemia, but infection was considered likely because of the presence of and excavated pulmonary nodule in one case and bronchiectasis in the other.

Eleven of the 50 patients (22%) experienced flare (median DAS score 4.6, range 3.2–7) and received retreatment with a second cycle of rituximab at 6 months. During the followup, 30 additional patients had flare after the initial period of 6 months and the median delay of retreatment among the 41 responders (taking into account those retreated at 6 mo) was 9 months (range 6–24). The longest delay before retreatment was 24 months, but 3 patients, still doing well, were not retreated after this followup. There was no difference for frequency of retreatment between the 2 groups of patients with RA. No difference in terms of delay before retreatment could be determined regarding the type of initial response. Nine patients (18%) had no response to rituximab.

DISCUSSION

We describe our daily practice experience of the use of ritux-

Table 1. DAS28 and CRP changes at Week 24 with rituximab therapy.

Study Group	DAS28, median (range), <i>n</i> (%) > 5.1; Week 0	DAS28, median (range), <i>n</i> (%) > 5.1; Week 24	CRP, mg/l, median (range); Week 0	CRP, mg/l, median (range); Week 24
All patients, <i>n</i> = 50	5.66 (4.2–8.7); 38 (76)	3.97 (1.5–7)*; 14 (28)*	19 (1–292)	10 (1–99)*
Refractory to anti-TNF-α, <i>n</i> = 30	6.3 (4.7–8.7) 25 (83)	3.83 (1.5–6.5)*; 8 (27)*	18 (1–292)	8 (1–99)*
Contraindication to anti-TNF-α, <i>n</i> = 20	5.5 (4.2–6.7); 13 (65)*	3.9 (1.8–7)*; 6 (30)*	21 (5–153)	10 (1.8–72)*

DAS28: Disease Activity Score 28; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein (normal range < 1 mg/l). * *p* < 0.05 versus baseline.

Table 2. EULAR responses at Week 24 following rituximab therapy. Data are n (%) or median (range).

Study Group	EULAR Response (good + moderate)	EULAR Good Response	Remission	Failure	Retreatment at 6 months	Delay in Case of Retreatment, median mo (range)
All patients, n = 50	41 (82)	18 (36)	6 (12)	9 (18)	11 (22)	9 (6–24)
Refractory to anti-TNF- α , n = 30	27 (90)	12 (40)	4 (13)	3 (10)	4 (13)	10 (6–24)
Contraindication to anti-TNF- α , n = 20	14 (70)	6 (30)	2 (10)	6 (30)	7 (35)	8 (6–18)

EULAR: European League Against Rheumatism; TNF- α : tumor necrosis factor- α .

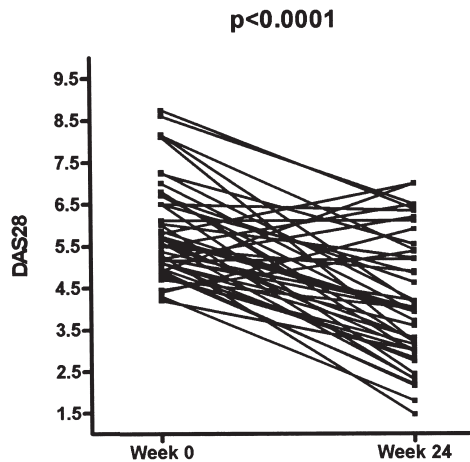


Figure 1. Individual changes in DAS28 after rituximab therapy.

imab in a cohort of patients with RA with multidrug-resistant disease. We previously reported our preliminary data in 18 patients¹⁰, but this series of 50 patients outside formal clinical trials is the largest reported to our knowledge. The principal new data provided by our study are (1) the report of daily practice results including older patients (58 vs 51 yrs) with longer disease duration (15 vs 10 yrs) and having received a higher number of previous DMARD (3.5 vs 2.5) in comparison with randomized controlled trials⁵; and (2) the original comparison of patients with previous failure of anti-TNF drugs to treatment-naïve patients. Our results show that substantial and durable clinical benefit can be achieved with a short course of rituximab in patients with active RA, in patients who have had either inadequate response or contraindication to previous anti TNF- α therapy, and with similar results in both cases.

Although our study was not powered to define the effectiveness of rituximab, the clinical improvements were in accord with or even higher than those observed in the 3 randomized controlled trials — considering the EULAR response, 83% to 85%³, 67% to 73%⁵, and 65%⁴. Some open-label studies also reported sustained efficacy, with 33% achieving American College of Rheumatology-50% (ACR50) response among 12 RA patients refractory to anti-TNF- α or DMARD at Week 28 after 4 weekly infusions of rituximab¹¹; 70% of good or moderate DAS28 response among 10 patients

refractory to at least one anti-TNF- α followed for 28 weeks¹²; and 60% of good or moderate EULAR response among 20 RA patients resistant to more than 2 anti-TNF drugs¹³. Tolerance was satisfying in our short-term study, as in published randomized trials^{4,5}, with occurrence of only 2 infections in patients at risk of infections. This further emphasizes the satisfactory safety profile of rituximab therapy, despite depletion of B cells in our older patients with longer disease duration in comparison to those included in randomized trials. This was confirmed in a recent longterm study¹⁴; as for immunoglobulin levels, measurements were not available in our patients, who were treated between 2004 and 2006, although it should be recommended to monitor them for longterm followup, as suggested⁸. Moreover, only one infusion-related reaction occurred; it has been suggested that the frequency and intensity of first infusion-associated events may be reduced by intravenous glucocorticoid premedication⁵ that is recommended as comedication⁸.

Among the unanswered questions about rituximab, the requirement for subsequent infusions remains undetermined. In our study, 11 patients (22%) had a loss of response before Week 24, and ultimately 41 patients were retreated (82%) because of clinical deterioration after a median of 9 months. Popa, *et al*¹⁴ reported a longer duration of benefit per cycle, but this may be explained by patient heterogeneity and also by the definition of clinical deterioration, which remains to be determined. This suggests that some patients may have sustained improvement without the need for repeated infusions, which is clinically important and could be cost-effective; further data are required to determine predictive factors of this benefit.

Our study has several limitations, as it was a descriptive study of patients with active RA treated according to their clinical characteristics and not a controlled trial; owing to limitations in the methodology, only general conclusions can be drawn. Moreover, the sample size did not allow accurate comparison between patients with and without RF, and the study was also underpowered to establish a definite comparison between RA patients with and without previous use of anti-TNF drugs. However, this large series of patients with RA who were older and had long disease duration — having taken a higher number of previous DMARD — together with previous series, provides reasonably accurate background information on outcome to support the data from randomized trials,

and the effectiveness and safety of rituximab in trial patients with RA.

In our daily practice study, a single course of 2 infusions of rituximab, in combination with continued MTX, provided significant improvement in disease activity at Week 24, with good tolerance, in patients with very severe and active RA despite previous use of anti-TNF- α agents or with contraindication to these drugs. Our findings provide further valuable insight and confirm data from clinical trials on the role of B cells in this disabling disease.

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