Effects of Early Rituximab Retreatment in Rheumatoid Arthritis Patients with an Inadequate Response After the First Cycle: Retrospective Arthritis Cohort Study

To the Editor:

The therapeutic options for rheumatoid arthritis (RA) have been significantly improved by the introduction of novel biological agents[1]. In this context the chimeric anti-CD20 monoclonal antibody rituximab (RTX) was approved for treatment of active and resistant RA in Germany in 2006. RTX was shown to represent a safe and effective treatment option over several courses leading to selective and transient depletion of the CD20+ B cell population[2-4]. However, to date the optimal timepoint for retreatment has not been defined exactly, and longterm treatment strategies using RTX have not been established.

Our observational cohort study was performed to compare different treatment strategies using RTX and especially the effects of early retreatment within 4 to 6 months after first drug administration with a retreatment interval of more than 6 months in patients with RA (Figure 1). Baseline characteristics of the 39 RA patients are shown in Table 1. The respective comorbidities included overlapping chronic rheumatic diseases in 8 cases (systemic lupus erythematosus, cutaneous lupus erythematosus, scleroderma, ankylosing spondylitis, and 4 patients with secondary Sjögren's syndrome). Patient histories revealed 2 cases of previous mycobacterial infections, a case of chronic hepatitis C infection, and 3 cases of malignant diseases.

For the first course of RTX, 39 patients received 2 doses of 1000 mg RTX (in one patient 2 × 500 mg RTX). For subsequent treatment courses, 27 patients received a second, 14 patients a third, 4 patients a fourth, and one patient a fifth RTX administration with the recommended premedication.

Four months after the first course of RTX, patients were classified according to their short-term behavior as classical responders [reduction of Disease Activity Score 28-joint count (DAS28) by > 1.2 and retherapy after 6 months], as nonresponders (no relevant reduction of DAS28 and retherapy after 6 months), and as patients requiring short-term retherapy (retherapy between 4 and 6 months after first RTX course). The reason for early retherapy was primary nonresponse to RTX in 3 cases and early relapses after significant response in the remaining 3 cases (Figure 1).

Subsequently, followup data of the same patients were evaluated for their DAS28 response and reduction of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) 4 months after the second RTX course.

The results were as follows. Longterm efficacy was evaluated 4 months after baseline of the second RTX cycle. In the group of classical responders (n = 19), after the first RTX course, a significant reduction was also evident in the DAS28, from 5.82 ± 0.98 to 3.8 ± 1.43 ($p < 0.0002$, Mann-Whitney test), in the longterm evaluation. Further, a significant reduction of ESR (from 33.8 ± 16.9 mm/h to 17.0 ± 10.9 mm/h; $p < 0.0096$) and a numerical reduction of CRP (from 5.3 ± 7.9 mg/dl to 1.2 ± 1.7 mg/dl; $p < 0.0671$) were observed (Figure 2).

In the group of patients defined as nonresponders (n = 14) after the first RTX course, a significant reduction of DAS28 from 5.1 ± 1.2 to 3.4 ± 1.45 ($p < 0.0109$) was also observed 4 months after the second cycle of RTX. However, the reduction of the CRP and ESR values was not significant compared to baseline levels (Figure 3).

In the group of patients with early RTX retreatment between months 4 and 6 (n = 6) after the first cycle, there was a significant reduction of DAS28, from 6.5 ± 1.0 to 2.77 ± 0.95 ($p < 0.0043$), as well as a significant reduction of CRP values (7.45 ± 5.65 mg/dl to 1.62 ± 2.47 mg/dl; $p < 0.0317$) and ESR (from 51.2 ± 26.9 mm/h to 4.0 ± 3.26 mm/h; $p < 0.0095$; Figure 4).

In summary, our data show retreatment of classical RTX responders after 6 months was associated with a good longterm result in DAS28 improvement as well as CRP and ESR reduction. In patients characterized as primary nonresponders, retreatment after 6 months showed limited efficacy, with relevant reduction of DAS28 but not in CRP and ESR levels.

Notably, our preliminary results also indicate that a favorable effect can be achieved by early retreatment of nonresponders to a first RTX cycle. Due to the limited number of patients in our study, further investigations in larger cohorts are required to substantiate this observation.

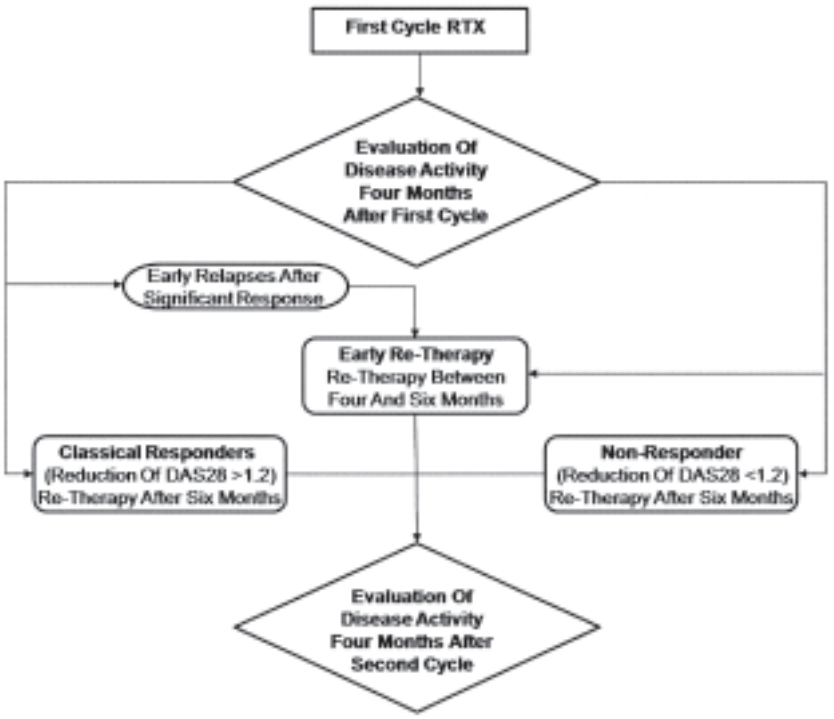

Figure 1. Progress of patients through treatment.

Table 1. Baseline demographic characteristics of the observational cohort. Data are mean ± SD or number (%).

Characteristics	Classic Responders	Nonresponders	Short-term Re-therapy
Age, yrs*	55.05 ± 9.79	52.00 ± 10.49	45.00 ± 16.00
Female, %**	78.95	71.43	83.33
Disease duration, yrs*	10.89 ± 7.43	15.79 ± 16.75	8.67 ± 6.31
Rheumatoid factor and/or ACPA-positive, %**	89.47	85.71	66.67
Radiographic erosive disease, n (%)**	10 (52.63)	9 (64.29)	3 (50.00)
Radiographic non-erosive disease, n (%)**	3 (15.79)	2 (14.29)	3 (50.00)
Radiographic not specified, n (%)**	6 (31.58)	3 (21.43)	0 (0.00)
Previous DMARD, more than one, n (%)**	10 (52.63)	10 (71.42)	5 (83.33)
Previous DMARD, one, n (%)**	4 (21.05)	1 (7.14)	1 (16.66)
Previous DMARD, none or not specified, n (%)**	5 (26.32)	3 (21.43)	0 (0.00)
Previous biologics, more than one anti-TNF agent, n (%)**	10 (52.63)	6 (42.86)	5 (83.33)
Previous biologics, one anti-TNF agent, n (%)**	9 (47.37)	5 (35.71)	1 (16.66)
Previous biologics, IL-1 receptor antagonist, n (%)**	3 (15.79)	1 (7.14)	0 (0.00)
Previous biologics, none or not specified, n (%)**	4 (21.05)	3 (21.43)	0 (0.00)
Extraarticular manifestation of RA, n (%)**	5 (26.32)	7 (50.00)	1 (16.66)
Rheumatoid nodules, n (%)**	4 (21.05)	7 (50.00)	1 (16.66)

* No significant differences between groups (Mann-Whitney U test); ** No significant differences between groups (chi-square test). ACPA: anti-citrullinated protein/peptide antibodies; DMARD: disease-modifying antirheumatic drug; IL: interleukin; TNF: tumor necrosis factor.

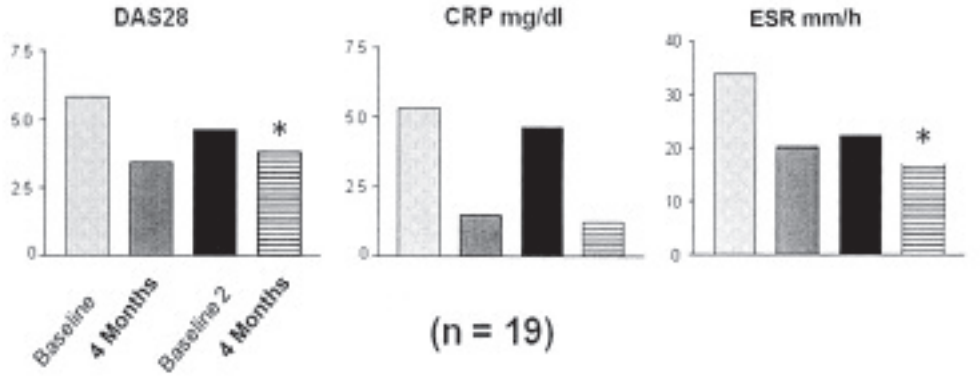

Figure 2. Clinical characteristics of classical responders to treatment: reduction of DAS28 by > 1.2 and retherapy after 6 months. *Significant reduction.

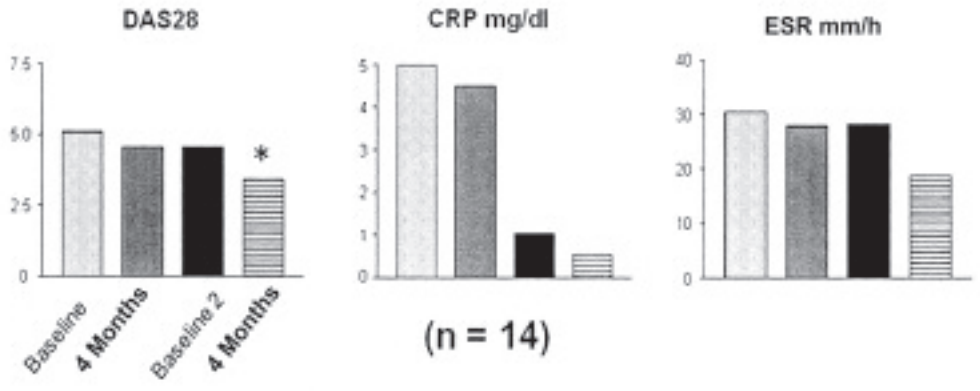

Figure 3. Clinical characteristics of nonresponders: no relevant reduction of DAS28 and retherapy after 6 months. *Significant reduction.

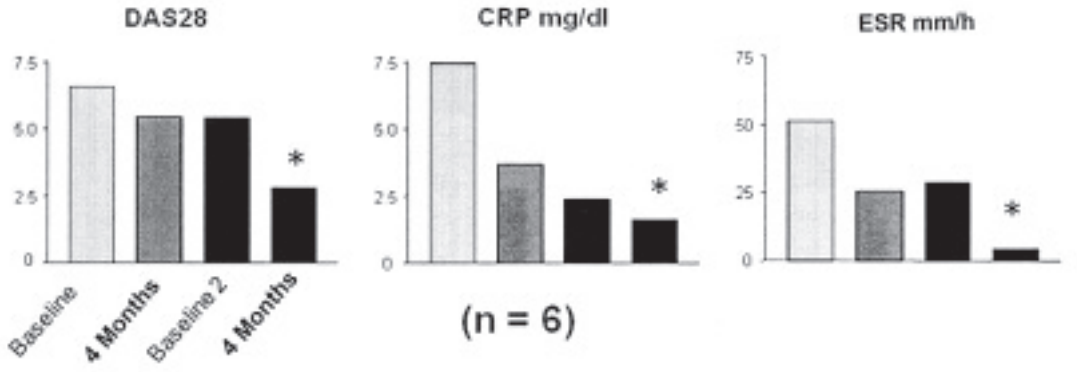

Figure 4. Clinical characteristics after short-term retherapy (between 4 and 6 months after first RTX course). *Significant reduction.

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