Targeted therapies in rheumatoid arthritis
Boumans, M.J.H.

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CHAPTER 6

Biological treatment of rheumatoid arthritis: Towards a more cost-effective retreatment regimen using rituximab?

M.J.H. Boumans MD, K. Vos MD PhD, D.M. Gerlag MD PhD, P.P. Tak MD PhD

1Academic Medical Center/University of Amsterdam, Amsterdam, the Netherlands

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Treatment with rituximab may reduce disease activity in patients with rheumatoid arthritis (RA). The current dosing schedule of rituximab 2x1000 mg has been shown to induce and maintain a clinical response in initial responders, and is also protective against progression of joint destruction.\(^1\) Recently, the treatment schedules of 2x1000 mg and 2x500 mg rituximab were compared side-by-side in early active RA patients.\(^4\) It was shown that only initial treatment with 2x1000 mg rituximab resulted in statistically significant protection against progression of structural damage, whereas 2x500 mg and 2x1000 mg resulted in comparable clinical efficacy. Exploratory analysis suggested that retreatment with 2x500 mg rituximab after 6 months might be protective in terms of inhibition of structural damage. Induction therapy with 2x1000 mg rituximab followed by retreatment with 2x500 mg or 1x 1000 mg after 6 months could be a very cost effective approach.

In this open pilot study, patients with RA\(^5\), who were previous anti-TNF inadequate responders with a moderate or good response to initial treatment with 2 x 1000 mg rituximab according to the EULAR response criteria\(^6\) were included when their last treatment with 2 x 1000 mg rituximab was at least 24 weeks ago and when they had a DAS28 of \(\geq 2.6\). At baseline, patients were retreated with 1 x 1000 mg rituximab. Patients were followed up for 48 weeks with monthly assessments of the DAS28. When the DAS28 was \(\geq 2.6\) after at least 24 weeks of follow-up, patients received a second retreatment with 1 x 1000 mg rituximab. Radiographs of hands and feet obtained at baseline and at week 48 were evaluated using the Sharp-van der Heijde scoring method (SHS; range 0-448).\(^7\)

Nine patients were included, baseline characteristics are shown in Table 1. Throughout 48 weeks of follow-up, the mean DAS28 did not reach the baseline level (4.10) at any visit, meaning that the clinical response was sustained (Figure 1A and 1B). The mean change in total SHS after 1 year was -1.5 (± 2.8), indicating there was no progression of structural damage after retreatment with 1 x 1000 mg rituximab on the group level.

Two out of nine patients showed some progression of structural damage, their SHS score increased with 2 points in 48 weeks (Figure 1C). Of note, for one of these two patients, this increase was only seen in the joint space narrowing score (data not shown).

The results suggest that both the clinical response and the inhibition of structural damage induced by 2 x 1000 mg rituximab might be sustained in most RA patients by retreatment with 1 x 1000 mg rituximab rather than with the current retreatment regimen of 2 x 1000 mg. A limitation of this study is obviously the small sample size. However, this open pilot study provides the rationale for larger clinical trials, also in earlier, less therapy-resistant disease, evaluating new dosing regimens for the retreatment of RA patients with rituximab. If confirmed, induction therapy with 2 x 1000 mg rituximab followed by systematic retreatment with 1 x 1000 mg in case of disease activity after 24 weeks could provide a very patient-friendly and cost-effective biologic treatment regimen. It is also tempting to speculate that retreatment with dosages lower than the currently approved dosing regimen could have an advantage in terms of safety, but this needs to be shown in future studies.
Figure 1. Clinical follow-up and radiographic outcome after retreatment with 1x1000 mg rituximab. A. The mean change from baseline (± SD) in DAS28 at every study visit. The dotted line represents the level of the mean DAS28 at baseline: 4.10. B. The DAS28 at every study visit. Each line represents the follow-up of one patient. C. The change in total Sharp-van der Heijde scoring method (SHS) after 48 weeks. Each line represents the change of 1 patient. (RTx= rituximab, D=Day, W=Week)

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