B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
Thurlings, R.M.

Citation for published version (APA):
RE-TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS WHO WERE INITIAL NONRESPONDERS TO RITUXIMAB: COMMENT ON THE ARTICLE BY THURLINGS ET AL.
RE-TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS WHO WERE INITIAL NONRESPONDERS TO RITUXIMAB: COMMENT ON THE ARTICLE BY THURLINGS ET AL.

To the Editor

In a recent article, Thurlings et al reported the efficacy of subsequent cycles of rituximab in rheumatoid arthritis (RA) patients whose disease had failed to respond to the first course of treatment. The authors have previously demonstrated that clinical nonresponse to rituximab is associated with the persistence of B-lineage cells in the synovium. This is consistent with the findings of our own studies and the studies of other investigators on synovium. It is also consistent with the results of our studies of peripheral blood. In fact, we have never observed nonresponse in patients with fast and complete B cell depletion, as measured by highly sensitive flow cytometry. These findings suggest that patients whose RA fails to respond to 1 cycle of rituximab may have a form of disease that potentially would be treatable via B cell depletion, if depletion were enhanced. Administering a second cycle of rituximab after a relatively short interval might be one potential strategy to enhance depletion. However, Thurlings et al concluded that a lack of response after 2 cycles of rituximab may indicate a B cell-independent pathogenic mechanism. This conclusion requires the demonstration that depletion becomes complete following the second cycle of rituximab. In some patients, depletion may be even less efficient after subsequent cycles of rituximab, due to the development of human antichimeric antibodies. No data describing peripheral blood or synovial depletion were presented in the report by Thurlings and colleagues. Interpreting clinical responses in patients with highly resistant RA can be difficult. In the study by Thurlings et al, a small number of patients with a persistent lack of response were selected from a population with highly resistant RA. A comparison of baseline clinical characteristics between responders and nonresponders may have been helpful. Data on the components of the Disease Activity Score in 28 joints (DAS28) and absolute DAS values in the group of nonresponders before and after each cycle would have been interesting to compare with the data that were presented for responders.

The question of the mechanism of nonresponse to rituximab is crucial to our understanding of the role of B cells in RA. While an assessment of the clinical efficacy of subsequent cycles of rituximab in nonresponders is valuable, it may be premature, with only limited clinical data and no data regarding blood or synovial depletion, to draw conclusions about the pathogenesis of disease in this group.

REFERENCE

(6) Prevos ML, van’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with RA.
B Cells and B Cell directed therapies in Rheumatoid Arthritis

Page 5

...of peripheral blood CD19+ B cell depletion and HACA formation were not related to the clinical response. Hence, the extent of peripheral blood CD19+ B cell depletion and HACA formation were not related to the clinical response. Taken together, our data suggest that re-treatment of initial nonresponders is not likely to induce a robust clinical response after a second course of rituximab. The mechanism of nonresponse needs further study.

**FIGURE No.2**

**FIGURE 1.** Disease Activity Score in 28 joints (DAS28) after 2 treatment courses (crse) in individual rheumatoid arthritis patients who experienced no decrease after the second treatment course. No significant changes in the DAS28 were observed after re-treatment.