B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
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RE-TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS WHO WERE INITIAL NONRESPONDERS TO RITUXIMAB: COMMENT ON THE ARTICLE BY THURLINGS ET AL.

CHAPTER 10
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 with no data regarding blood or synovial depletion, to draw conclusions about the pathogenesis of disease in this group.

REPLY

To the Editor

We thank Dr. Vital and colleagues for their comments on our recent article regarding the re-treatment of initial nonresponders to rituximab. We completely agree with their suggestion that, in patients whose RA does not respond to repetitive treatment courses with rituximab, synovitis might be driven either by B cell–independent pathogenic mechanisms or by persistent B-lineage cells, as discussed in our report. The exact mechanism has not been eluci-

REFERENCE


(6) Prewo ML, van’t Hof MA, Kuper HII, 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 rheumatoid arthritis.
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could be detected in 5 of 22 patients (4 responders and 1 nonresponder). After the second treatment course, small numbers of CD19+ B cells (0.01 * 10^9/liter) could be detected in 5 of 22 patients (4 responders and 1 nonresponder). We also analyzed antirituximab antibody formation (human antichimeric antibodies [HACAs]), using a previously described assay. HACAs were observed in serum (obtained when rituximab was at trough levels before the second course) in 2 of 30 patients. Two of these patients experienced a moderate response (according to the EULAR criteria) to the first treatment course, and 1 patient did not respond. During the infusion of the second rituximab course, 1 patient (an initial responder) experienced a serious infusion-related reaction, and rituximab treatment was discontinued. The other 2 HACA-positive patients experienced the same clinical response after the second treatment course (1 moderate responder and 1 nonresponder). 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.

The DAS28 responses in the individual patients who were initial nonresponders are shown in Figure 1. After the first treatment course (1 moderate responder and 1 nonresponder). 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.

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FIGURE

FIGURE 1. Disease Activity Score in 28 joints (DAS28) after 2 treatment courses (crse) in individual rheumatoid arthritis patients who were initial nonresponders to rituximab treatment. No significant changes in the DAS28 were observed after re-treatment.