B cells and B cell directed therapies in rheumatoid arthritis: towards personalized medicine
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Chapter 10

B Cells and B Cell directed therapies in Rheumatoid Arthritis

RE-TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS WHO WERE INITIAL NONRESPONDERS TO RITUXIMAB: COMMENT ON THE ARTICLE BY THURLINGS ET AL.
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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 1. The authors have previously demonstrated that clinical nonresponse to rituximab is associated with the persistence of B-lineage cells in the synovium 2. This is consistent with the findings of our own studies 3 and the studies of other investigators 4 on synovium. It is also consistent with the results of our studies of peripheral blood 5. In fact, we have never observed nonresponse in patients with fast and complete B cell depletion, as measured by highly sensitive flow cytometry 6. 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) 7 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.

REFERENCE

6. Prevoo ML, van ’t Hof MA, Kuper HH, van Leeuwen MA, van ’t 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...
dated. It would be of interest to analyze whether pathogenic B-lineage clones persist in nonresponders after multiple treatment courses with rituximab, but such data are, as yet, unavailable. Alternatively, B-cell–independent mechanisms may be involved in nonresponders, but this question also has yet to be answered. In this situation, nonresponse might occur in patients who exhibit complete B cell depletion. Our cohort consisted of 30 patients with RA treated with repetitive courses of rituximab, using a disease activity based re-treatment schedule. Patients were re-treated after at least 6 months if their DAS28 was ≥ 3.2. A clinically significant decrease in disease activity was defined as a moderate or good response (according to the European League Against Rheumatism [EULAR] criteria), as measured during monthly study visits occurring for at least 2 consecutive months. Results showed no trend toward differences between responders and nonresponders in baseline characteristics (sex, age, presence of erosions, rheumatoid nodules, baseline methotrexate or prednisone dosage, number of previous biologic agents received, disease duration, baseline DAS28 overall or components, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] level, and presence or titer of IgM rheumatoid factor and anti–citrullinated peptide antibodies). Thus, nonresponders could not be identified using baseline clinical characteristics.

The DAS28 responses in the individual patients who were initial nonresponders are shown in Figure 1. After the first treatment course, nonresponders experienced no change in the DAS28, ESR, CRP level, tender joint count, or swollen joint count. In contrast, all of these parameters decreased in responders (P < 0.01 for all). After the second treatment course, initial responders to rituximab experienced a further decrease in the DAS28 (P = 0.012), ESR (P = 0.012), CRP level (P = 0.017), tender joint count (P = 0.046), and swollen joint count (P = 0.022), whereas initial nonresponders experienced no decrease in any of the parameters after the second treatment course. Using fluorescence-activated cell sorting, we analyzed 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 were initial nonresponders to rituximab treatment. No significant changes in the DAS28 were observed after re-treatment.