

EDITORIALS



Rituximab in ANCA-Associated Disease

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Antineutrophil cytoplasmic autoantibodies (ANCA) are serologic markers of small-vessel vasculitides, including microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's granulomatosis), and the Churg–Strauss syndrome.¹ Since the discovery of ANCAs more than two decades ago, substantial clinical, in vitro, and in vivo data have shown that ANCAs that are specific for myeloperoxidase, and probably ANCAs that are specific for proteinase 3, participate in the pathogenesis of small-vessel vasculitis.² These autoantibodies activate neutrophils and monocytes, resulting in damage to the vascular endothelium. Although ANCAs alone are sufficient to cause disease in animal models, additional genetic, epigenetic, and environmental pressures modulate disease in patients and amplify and alter the disease phenotype, which leads to the protean manifestations of this once deadly disease. Thus, it is not surprising that B-lymphocyte-directed therapy that decreases the ANCA titer has a salutary effect on ANCA-associated disease. In addition to eliminating antibody-producing cells, anti-B-cell therapy may have a more general effect on the immunopathogenesis of autoimmune disease by altering B-cell and perhaps T-cell regulatory function. This possibility provides the basis for the as yet untested hypothesis that anti-B-cell therapies may diminish the propensity for relapse in some patients with ANCA-associated disease.

In this issue of the *Journal*, two pivotal articles examine the efficacy of anti-B-lymphocyte therapy in the induction phase of treatment of ANCA-associated disease. Jones et al. report on the results of a randomized trial of rituximab versus cyclophosphamide in ANCA-associated renal vas-

culitis (RITUXIVAS) (Current Controlled Trials number, ISRCTN28528813),³ and Stone et al. report on the results of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (ClinicalTrials.gov number, NCT00104299).⁴ Similar conclusions are reached in the two studies. Both trials showed that rituximab was efficacious in inducing a remission, as compared with intravenous cyclophosphamide (in the RITUXIVAS trial) or oral cyclophosphamide (in the RAVE trial).

There are a number of important differences between the two trials. In the RITUXIVAS trial, patients who were randomly assigned to the rituximab group also received at least two doses of intravenous cyclophosphamide, whereas in the RAVE trial, patients randomly assigned to the rituximab group did not receive any cyclophosphamide. The trials were similar in that all patients in both trials received both intravenous and oral glucocorticoid therapy.

Whether cyclophosphamide should or should not be used in conjunction with rituximab for the induction of a relapse-free, sustained remission is a critical question. Investigators in the RITUXIVAS trial reported sustained remission for 12 months, whereas outcome data from the RAVE trial were reported only on the 6-month remission-induction period. The RAVE trial data were confounded by the use of glucocorticoid therapy for 5 of the 6 months of follow-up. Long-term data from the RAVE trial should answer the critical question of the duration of remission and the incidence of relapse among patients who did not receive any cyclophosphamide but received rituximab and glucocorticoid therapy alone.

We are in an era in which the efficacy of our therapeutic armamentarium results in a reduction

of disease activity, but at the risk of serious adverse events. Both trials raise the specter of substantial complications from the use of rituximab and other immunomodulating agents in ANCA-associated disease. Fewer adverse events would have been expected in patients treated with rituximab as compared with oral cyclophosphamide. Unfortunately, in the RAVE trial, the rate of adverse events was equivalent in the two study groups. This finding is of additional concern because the RAVE trial used oral cyclophosphamide in the control group rather than the similarly effective yet less toxic intravenous cyclophosphamide therapy.⁵ Similarly, in the RITUXIVAS study, 6 of 33 patients in the rituximab group died, as did 2 of 11 patients in the control group. Although the rate of death was similar between the two groups, this high rate of death early in the course of disease is of great concern. Adverse events associated with many of the currently available biologic agents, including anti-CD20 therapies, have the risk of progressive multifocal leukoencephalopathy⁶ and an increase in the overall risk of infections.^{7,8} The RAVE trial also showed an unexpectedly elevated number of malignant conditions detected over a relatively short treatment period. These adverse events challenge us to decrease the cumulative exposure to immunosuppressive agents in patients with relapsing and remitting disease.

The practical implications of these two studies are substantial. Rituximab might be considered as an option for first-line therapy for induction of remission of ANCA-associated disease. It remains unclear whether rituximab should be used with glucocorticoids alone or in combination with intravenous cyclophosphamide. Cyclophosphamide therapy has a proven track record of inducing sustained remission. At this juncture, the 6-month follow-up of the RAVE trial does not provide an answer to the question of whether anti-B-cell therapy and glucocorticoids will result in a sustained remission. The RAVE trial does provide additional guidance for patients with disease relapse after previous therapy. Here, rituximab was superior to oral cyclophosphamide for the induction of remission in relapsing disease.

Another critical and practical consideration is the need for maintenance immunosuppressive

therapy. During the 12-month follow-up in the RITUXIVAS trial, patients received azathioprine as standard therapy to maintain remission.⁹ Although many patients require long-term immunosuppressive therapy to prevent relapsing disease, some practitioners discontinue or substantially reduce therapy to maintain remission in patients with a reduced propensity for relapse.¹⁰ The important unanswered question is whether anti-B-cell therapy will alter the immunopathogenetic process, permitting the discontinuation or reduction of therapy to maintain remission. Here again, understanding the basic pathogenetic mechanisms of ANCA-associated disease should inform the development of reliable biomarkers of remission and relapse so that physicians will know when to initiate, discontinue, or reduce the use of immunomodulating drugs. For now, RITUXIVAS and RAVE lend hope for our patients that targeted therapy may quell this B-cell-driven autoimmune disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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