Rituximab or Cyclophosphamide in ANCA-Associated Renal Vasculitis

TO THE EDITOR: In the studies by Jones et al.[1] and Stone et al.[2] (July 15 issue), the effectiveness of treatment of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides with either a rituximab-based regimen or a cyclophosphamide-based regimen was similar. Although long-term results are lacking, these studies add rituximab as a valuable therapeutic option. However, approximately one third of patients still did not achieve remission. In other studies, predictors of treatment failure such as alveolar hemorrhage or severe kidney disease have been identified.[3-5] Since these patients might benefit from a more intense or prolonged immunosuppression, it would be of interest to know whether predictors of treatment failure can be identified.

In the study by Stone et al., remission was achieved with similar frequency among patients with newly diagnosed disease (60% in the rituximab group and 65% in the control group) and patients with relapsing disease (67% in the rituximab group). The low remission rate among patients with relapsing disease in the control group (42%) warrants further exploration. Which organ manifestation persisted? Was there a relationship between treatment failure and the type of previous immunosuppressive therapy? The long-term results will answer the question of whether rituximab will become the first choice for therapy.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The randomized trial of rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS; Current Controlled Trials number, ISRCTN28528813) reported on by Jones et al. provides us with much needed controlled data on the use of an expensive biologic drug in a rare disease. Despite the positive findings in open studies, the authors were not able to show a benefit of early rituximab treatment, and they even report a doubling of the rate of early death in the rituximab cohort as compared with the control group (18% vs. 9%). Although this finding may not reach statistical significance because of low numbers, clinicians would (and should) be much concerned about such figures when advising patients about the preferred course of action. Whether this increased rate of early death is due to the study design (e.g., patient selection and no other immunosuppression after two intravenous cyclophosphamide treatments) or other unexplained problems with rituximab is not clear. My colleagues and I think that the early mortality issues should have been discussed in greater detail.

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Dr. Nossent reports receiving speaking and travel fees from Roche, Abbott, and Schering-Plough. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: The Rituximab in ANCA-Associated Vasculitis (RAVE; ClinicalTrials.gov number, NCT00104299) and RITUXVAS trials provide plausible evidence that rituximab is effective in ANCA-associated vasculitis. However, there are important concerns.

The design of the RAVE trial biased the outcome in favor of rituximab, because 52% of the patients in the rituximab group had recurrent ANCA-associated vasculitis. These recurrences were probably due to cyclophosphamide failures, perhaps because of abnormal cyclophosphamide metabolism. Evidence of this bias is that for recur-

rent ANCA-associated vasculitis, the success rate of rituximab versus cyclophosphamide was 67% versus 42%; for new ANCA-associated vasculitis, the success rate was 61% versus 63%. This bias probably also affected the secondary outcomes.

Neither the RAVE nor the RITUXVAS trial made clear which manifestations of ANCA-associated vasculitis accounted for the differences in Birmingham Vasculitis Activity Scores. These differences may have involved manifestations of ANCA-associated vasculitis that were less clinically important than those in the kidney or lung; the latter manifestations were not different between rituximab and cyclophosphamide in the RAVE trial. Also, the quantitative level of proteinuria, arguably the best measure of glomerular healing, was not reported.

The follow-up period of the RAVE and RITUXVAS trials was short. Longer follow-up is needed to determine whether rituximab is of value and whether it is a good value (rituximab is much more expensive than oral cyclophosphamide).[1,2]

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No potential conflict of interest relevant to this letter was reported.

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2. Hebert LA, Rovin BH. Oral cyclophosphamide is on the verge of extinction as therapy for severe autoimmune disease (especially lupus): should nephrologists care? Nephron Clin Pract 2010 August 3 (Epub ahead of print).

TO THE EDITOR: Two randomized, controlled trials examined the efficacy and safety of rituximab in ANCA-associated vasculitides, as compared with cyclophosphamide, the standard therapy for remission induction in these immune-mediated diseases.[1] We believe that the safety issues warrant further discussion. Both trials raise concern in view of the substantial complications observed among patients with exposure to rituximab. In the RAVE trial, an unpredicted increase in the number of malignant conditions was reported in 6 of 124 patients who received rituximab (5%), although the comparison with 1 of 73 patients who did not have exposure to rituximab was not significant (1%). The finding of malignant conditions suggests the need for caution, since this trial used oral cyclophosphamide in the control group rather than the less toxic intravenous regimen.[1] Likewise, in the RITUXVAS trial, the two malignant conditions observed developed in patients who were treated with rituximab. Six of the 33 patients who received rituximab died, as did 2 of 11 patients in the control group. Even if the rate of death was similar in the two groups, this high rate of death early in the course of disease is of great concern. The high rates of adverse events detected over a relatively short treatment period are also of concern and warrant long-term safety studies of rituximab in vasculitides.

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No potential conflict of interest relevant to this letter was reported.

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DRS. JONES AND JAYNE REPLY: In the RITUXVAS trial, 6 of 33 patients in the rituximab group (18%) and 1 of 11 patients in the control group (9%) had died at 1 year. This difference is nonsignificant, and after 2 years, the mortality trends were reversed — ~~6~~ of 33 patients in the rituximab group (18%) and 3 of 11 patients in the control group (27%). We included elderly patients with severe renal dysfunction who were the most vulnerable to death. The 1-year mortality in the rituximab group was identical to that in a large retrospective outcome study involving 246 patients with ANCA-associated renal vasculitis.[1] During the first 2 weeks of treatment, the rituximab group received the same two doses of cyclophosphamide and high-dose glucocorticoids as the control group, and most severe adverse events and deaths occurred in the first 12 weeks after the onset of treatment. We have concluded that strategies to reduce the early high doses of glucocorticoids might improve the safety of vasculitis treatment.

The nonsignificant yet higher numbers of malignant conditions observed in the rituximab groups than in the control groups in both the RITUXVAS and RAVE trials warrant further investigation. However, it is difficult to attribute

such early malignant conditions to rituximab given the known association of malignant conditions with vasculitis at the time of diagnosis.[2] At our hospital, we have followed 83 consecutive patients with ANCA-associated renal vasculitis who were treated with rituximab for relapsing disease for a total of 262 patient-years. Cancer has developed in three of them: one breast carcinoma, one peritoneal malignant condition, and one recurrent basal-cell carcinoma. This rate of malignant conditions is similar to that observed with other treatments for ANCA-associated renal vasculitis, and our results in refractory ANCA-associated renal vasculitis[3] are consistent with studies of rituximab in rheumatoid arthritis in which increased rates of malignant conditions have not been observed.[4] Longer follow-up will be important to determine both the safety and efficacy of rituximab-based regimens.

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Since publication of their article, the authors report no further potential conflict of interest.

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DRS. STONE AND SPECKS REPLY: Schönermarck and colleagues ask about predictors of treatment failure, particularly the possibility that alveolar hemorrhage or severe renal disease portended a poorer prognosis in our study. We reported on both of these disease subgroups carefully. Neither constituted a risk factor for treatment failure — patients with alveolar hemorrhage or severe renal disease were just as likely to have a response to the combination of rituximab and glucocorticoids as to the combination of cyclophosphamide and glucocorticoids. Among patients who did not reach the primary outcome, there was no consistent pattern to organ-system involvement.

Hebert et al. raise the possibility that differences in the metabolism of cyclophosphamide accounted for the treatment differences among patients with relapsing disease. We do not believe that this is the case, because patients with disease that had previously been refractory to cyclophosphamide were excluded from the RAVE trial; it would not have been ethical to randomly assign such patients to that drug. Although approximately 40% of the patients enrolled in the trial had received cyclophosphamide for the treatment of earlier disease flares, all those patients had a response to that medication before. To our knowledge, there is no evidence that patients who had a response once to cyclophosphamide are less likely to have a response a second time.

Karassa sounds a note of caution about adverse events, particularly the occurrence of malignant conditions. We addressed this point in detail both in the article and in the Supplementary Appendix for the article, available at NEJM.org. As we noted in the Supplementary Appendix, "the attribution to any single drug of 'cause' for these cancers, which are common in the general population, is confounded by the fact that most patients have been exposed to multiple drugs known to be associated with an increased risk of cancer."

The 6-month, primary-outcome results of the RAVE trial provide support for rituximab as an important and viable treatment option for remission induction in ANCA-associated vasculitis. Many physicians will view rituximab as the standard of care because of the potential for fewer long-term adverse effects, particularly those pertaining to fertility and malignant conditions. We agree with all of the correspondents who note the importance of long-term follow-up in understanding the full role of rituximab in the treatment of ANCA-associated vasculitis. Long-term data on outcomes among all patients up to 18 months after enrollment in the RAVE trial are currently being analyzed.

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Since publication of their article, the authors report no further potential conflict of interest.