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Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

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ABSTRACT

BACKGROUND

The combination of cyclophosphamide and glucocorticoids leads to remission in most patients with antineutrophil cytoplasm antibody (ANCA)–associated vasculitides. However, even when patients receive maintenance treatment with azathioprine or methotrexate, the relapse rate remains high. Rituximab may help to maintain remission.

METHODS

Patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after a cyclophosphamide–glucocorticoid regimen were randomly assigned to receive either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22. The primary end point at month 28 was the rate of major relapse (the reappearance of disease activity or worsening, with a Birmingham Vasculitis Activity Score >0, and involvement of one or more major organs, disease-related life-threatening events, or both).

RESULTS

The 115 enrolled patients (87 with granulomatosis with polyangiitis, 23 with microscopic polyangiitis, and 5 with renal-limited ANCA-associated vasculitis) received azathioprine (58 patients) or rituximab (57 patients). At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio for relapse, 6.61; 95% confidence interval, 1.56 to 27.96; P=0.002). The frequencies of severe adverse events were similar in the two groups. Twenty-five patients in each group (P=0.92) had severe adverse events; there were 44 events in the azathioprine group and 45 in the rituximab group. Eight patients in the azathioprine group and 11 in the rituximab group had severe infections, and cancer developed in 2 patients in the azathioprine group and 1 in the rituximab group. Two patients in the azathioprine group died (1 from sepsis and 1 from pancreatic cancer).

CONCLUSIONS

More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine. (Funded by the French Ministry of Health; MAINRITSAN ClinicalTrials.gov number, NCT00748644; EudraCT number, 2008-002846-51.)

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*A complete list of additional investigators and members of the French Vasculitis Study Group who participated in the study is provided in the Supplementary Appendix, available at NEJM.org.

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Granulomatosis with polyangiitis (formerly called Wegener's granulomatosis), microscopic polyangiitis, and renal-limited antineutrophil cytoplasm antibody (ANCA)–associated vasculitides are the main ANCA-associated vasculitis variants.[1] Although these entities differ in their pathogenesis, genetics, and serotypes, severe forms of ANCA-associated vasculitis share several clinical features and currently have similar treatments.[2-6] A staged therapeutic strategy that combines glucocorticoids and cyclophosphamide to induce remission has dramatically improved survival over the past few decades, but with frequent early and late side effects. The results of two trials (RAVE and RITUXVAS) showed that rituximab was not inferior to daily oral or pulse intravenous cyclophosphamide for the induction of complete remission by 6 months and was associated with similar rates of adverse events.[3,4]

The maintenance of remission remains a major challenge.[7,8] In two previous studies of maintenance therapy, continuous cyclophosphamide treatment was compared with azathioprine[2] and azathioprine was compared with methotrexate (WEGENT trial).[5] The relapse rates in the former study were 13.7% in the cyclophosphamide group and 15.5% in the azathioprine group, at 18 months after diagnosis; in the latter study, the rates of relapse were 36% in the azathioprine group and 33% in the methotrexate group after a mean follow-up of 29 months after remission. In the RAVE study,[3] patients in rituximab-induced remission received no maintenance therapy, and those in cyclophosphamide-induced remission took azathioprine; at 18 months, the rates of relapse — 32% and 29%, respectively — and severity of disease flares were similar between the groups.[9]

Although the results of several retrospective studies have suggested that maintenance therapy with successive rituximab infusions for ANCA-associated vasculitides could be effective,[10,11] this approach has not yet been thoroughly evaluated. We conducted a nonblinded, randomized, controlled trial to compare systematic rituximab infusions and azathioprine, the standard-of-care therapy for remission maintenance in patients with granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis who are in remission after pulse cyclophosphamide–glucocorticoid induction therapy. We used a lower rituximab dose than that recommended to maintain remission of rheumatoid arthritis,[12] hypothesizing that this rituximab-based maintenance regimen would be more effective than and at least as safe as azathioprine.

Methods

Study Oversight

This trial, Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN), was designed by the two coprincipal investigators (the first and second authors), who also drafted and wrote the manuscript, with input as appropriate from coauthors and investigators at other sites (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The Hôpital Cochin Comité de Protection des Personnes (Paris) approved the study, which received legal, monitoring, and administrative management support from the Assistance Publique–Hôpitaux de Paris and was funded by the French Ministry of Health. The site investigators gathered the data, which were analyzed by the data analysis committee; the committee did not include representatives from Hoffmann–La Roche, which provided some of the rituximab for the study. Hoffmann–La Roche was not involved in or consulted about the study design, did not review the manuscript, and did not have access to the data or provide any other support for the study.

Patients

Eligible patients were 18 to 75 years of age and had newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after combined treatment with glucocorticoids and pulse cyclophosphamide. Patients had to be ANCA-positive at diagnosis or during the course of their disease; have histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis; or both.[13]

Remission was defined as a Birmingham Vasculitis Activity Score, version 3 (BVAS), of 0 (scores range from 0 to 63, with higher scores indicating more active disease).[13] Patients who had previously received rituximab or another form of biologic therapy were excluded. All patients provided written informed consent.

TREATMENT PROTOCOL

Remission-induction therapy included prednisone (starting at 1 mg per kilogram of body weight per day, followed by gradual tapering), preceded in some patients by methylprednisolone "pulses" (500 to 1000 mg daily for 1 to 3 consecutive days), and "pulse" cyclophosphamide (0.6 g per square meter of body-surface area on days 0, 14, and 28, then 0.7 g per square meter every 3 weeks for three to six additional pulses) until remission was attained, after 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, eligible patients were enrolled and randomly assigned, in a 1:1 ratio, to receive maintenance therapy with rituximab or azathioprine. Patients were assigned to groups centrally through computer-generated randomization, and randomization was stratified according to the disease-flare category, so that patients with relapsing disease would not exceed one third of the total enrollees. The patients, site investigators, and members of the data analysis committee were aware of the treatment assignments.

During the month after the last cyclophosphamide pulse, patients in the experimental (rituximab) group received intravenous rituximab (at a fixed 500-mg dose) on days 0 and 14 after randomization, and then at months 6, 12, and 18 after the first infusion. Patients in the control (azathioprine) group took azathioprine at a dosage of 2 mg per kilogram per day for 12 months, and then 1.5 mg per kilogram per day for 6 months and 1 mg per kilogram per day for 4 months. In addition, prednisone treatment was further tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left to each site investigator's discretion.

All patients were followed until month 28 (10 or 6 months, respectively, after the last rituximab infusion or azathioprine dose). *Pneumocystis jiroveci* pneumonia prophylaxis (400 mg of sulfamethoxazole and 80 mg of trimethoprim per day or pentamidine aerosolizations for patients allergic to sulfa drugs) was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic millimeter. The full protocol is available at NEJM.org.

STUDY ASSESSMENTS

Study visits were scheduled at enrollment, week 2, month 3, and every 3 months until the end point, at month 28 after randomization. At each study visit, the BVAS was recorded.[13] Patients were also asked to record their study medications weekly with the use of specifically designed diaries.

Blood samples were collected from all patients at each study visit. Serum samples were tested for ANCA by means of indirect immunofluorescence and tested for anti–proteinase 3 ANCA and antimyeloperoxidase ANCA with an enzyme-linked immunosorbent assay at randomization and then every 3 months until trial completion at month 28. Serum immunoglobulin levels were measured at inclusion, day 14, and months 6, 12, 18, 24, and 28, along with CD19+ B-lymphocyte counts for patients in the rituximab group.

END POINTS

The primary end point was the percentage of patients with major relapse (reappearance or worsening of disease with a BVAS >0 and involvement of at least one major organ, a life-threatening manifestation, or both) at month 28. Secondary end points included rates of minor relapse (reappearance or worsening of disease with a BVAS >0, not corresponding to a major relapse but requiring mild treatment intensification), rates of adverse events and their severity, and mortality.

Relapses were initially graded by each patient's site investigator; they were then reassessed and validated by the data committee, which included the two coprincipal investigators, as well as the second-to-last author and others from the Centre d'Epidémiologie Clinique, Hôpital Hôtel-Dieu, Paris. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.[14] Severe events were adverse events of grade 3 or 4, deaths (from any cause; grade 5), cancers, side effects necessitating hospitalization, or infusion reactions that contraindicated further infusions.

STATISTICAL ANALYSES

At 28 months after remission, the cumulative rate of major relapse in the WEGENT study was approximately 40%.[5] We hypothesized that rituximab would limit the number of major relapses at month 28 by an absolute difference of 25 percentage points. Under the assumption of 5% exclusion or dropout rates, with 80% statistical power and a two-sided alpha risk of 0.05, a total of 118 patients had to be enrolled in the trial.

Data were analyzed without knowledge of treatment assignments. Analyses were based on the

intention-to-treat principle for all patients except those who were included inappropriately or who withdrew their consent to participate early in the study. Quantitative variables were compared with the use of Student's t-test or the Wilcoxon rank-sum test, and categorical variables were analyzed with two-by-two tables or Fisher's exact test. Kaplan–Meier curves of the probability of remaining free of relapse were plotted for each treatment group, censored at death if it occurred before a relapse, and compared by means of a marginal Cox model stratified by disease type (newly diagnosed vs. relapsing disease). The bias-corrected and accelerated method was used to calculate a bootstrap confidence interval for the number needed to treat.[15]

RESULTS

PATIENTS AT RANDOMIZATION

Between October 2008 and June 2010, a total of 118 patients were enrolled in the study (Fig. 1). Three patients were excluded within 2 weeks after inclusion — 2 were not in remission, and 1 withdrew consent. The remaining 115 patients (58 in the azathioprine group and 57 in the rituximab group) (Table 1, and Table S1 in the Supplementary Appendix) included 87 with granulomatosis with polyangiitis, 23 with microscopic polyangiitis, and 5 with renal-limited ANCA-associated vasculitis; 92 were in remission after a first disease flare, and 23 were in remission after a relapse.

Induction treatment before enrollment included prednisone, at an initial mean (±SD) daily dose of 66.3±13.1 mg, and cyclophosphamide, with a total of 6.9±1.9 pulses and a mean cumulative dose of 7095±2341 mg. At remission, obtained after a mean of 4.6±2.8 months, and randomization, the mean daily prednisone dose was 17.6±7.3 mg. None of these treatment characteristics differed significantly between study groups.

STUDY END POINTS

Relapses

At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio, 6.61; 95% confidence interval [CI], 1.56 to 27.96; P=0.002). Hence, to avoid one major relapse, 4 patients (95% CI, 3 to 9) had to be treated with systematic rituximab infusions rather than with azathioprine. All patients who had a major relapse required changes to their immunosuppressive therapy, including prednisone-dose increases, according to investigators' best medical judgment. Eight patients in the azathioprine group had a relapse within the first 12 months of maintenance therapy (at 2 mg per kilogram per day), and 2 patients had a relapse between months 12 and 22; the remaining 7 relapses occurred after azathioprine treatment was stopped, between months 24 and 28. One patient in the rituximab group had a relapse at month 8, and the 2 others had a relapse after the last infusion, 1 at month 22 and 1 at month 24. Two of the 17 patients with a major relapse in the azathioprine group and none of the 3 patients with a major relapse in the rituximab group had discontinued prednisone before their relapse. Eight of the 17 patients in the azathioprine group, but none of the 3 patients in the rituximab group, had renal involvement when their major relapse occurred. Seventeen of the 20 patients with a major relapse had granulomatosis with polyangiitis, and 15 had newly diagnosed vasculitis.

Minor relapses occurred in nine patients in the azathioprine group (16%) and six patients in the rituximab group (11%) (P=0.43). Four patients in the azathioprine group had a minor relapse within the first 12 months of maintenance therapy, three between months 12 and 22 and the last two after azathioprine treatment was stopped. Six patients in the rituximab group had minor relapses before their last infusion, at months 6, 7, 12, 15, and 17, with the last at month 25. All relapses resolved with topical glucocorticoid treatment (for episcleritis or rhinitis) or transient increases in prednisone dose.

Figure 2 shows Kaplan–Meier curves for the probability of remaining free of major and global (major and minor) relapse. Descriptions of relapses and subgroup analyses are available in Tables S2 and S3 and Figures S1 through S4 in the Supplementary Appendix.

Severe Adverse Events

All the severe events are shown in Table 2, and Table S4 in the Supplementary Appendix. Severe infections developed in 8 patients in the azathioprine group (14%) and in 11 patients in the rituximab group (19%); some of these patients had normal immunoglobulin levels. Two patients in the azathioprine group, both with newly diagnosed granulomatosis with polyangiitis, died dur-

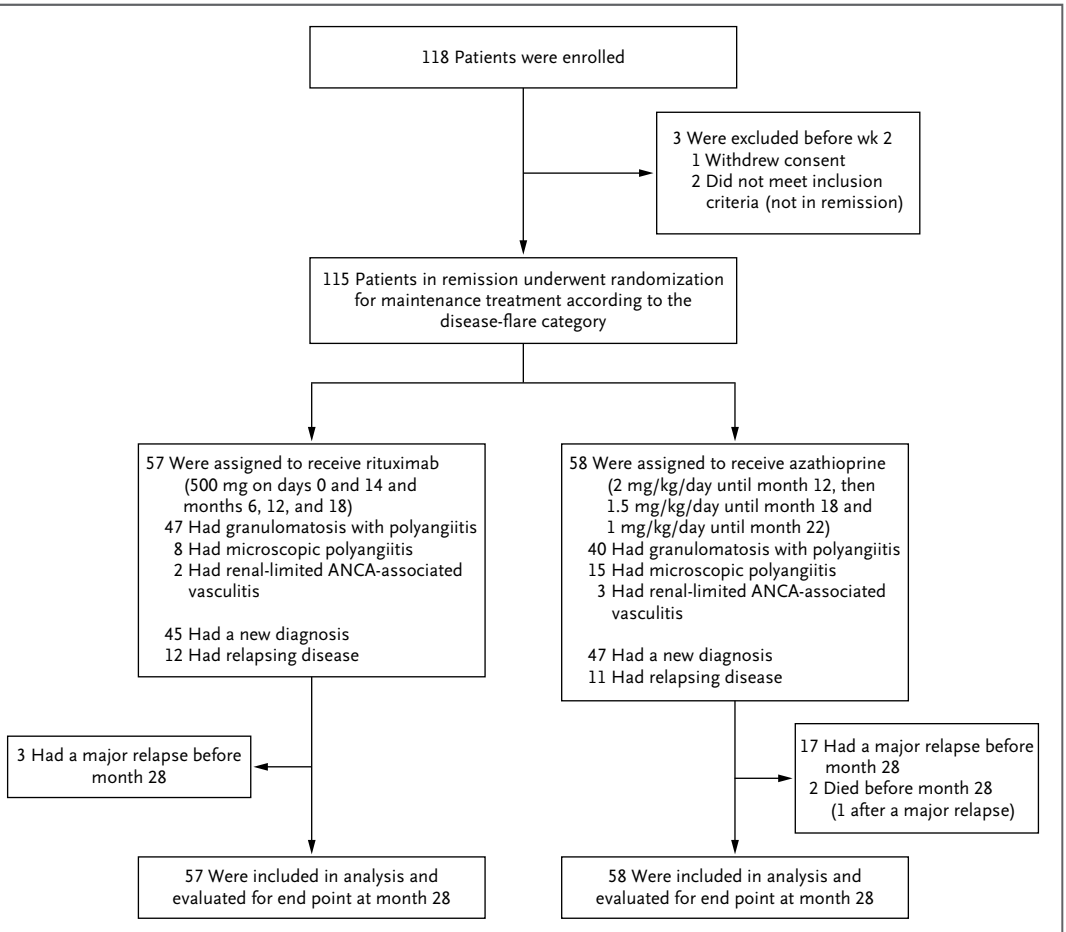

Figure 1. Randomization and Inclusion in the Analysis at Month 28.

Patients were randomly assigned, in a 1:1 ratio, to receive rituximab or azathioprine maintenance therapy. Randomization was stratified according to disease-flare category. The study groups were balanced with respect to vasculitis and antineutrophil cytoplasm antibody (ANCA)–labeling pattern and specificity. Three patients were excluded very early in the study (1 withdrew consent on the day of inclusion, and 2 were not in remission and therefore did not satisfy the main eligibility criterion). The remainder and majority of patients (58 in the azathioprine group and 57 in the rituximab arm) completed the 28 months of the trial and were included in the final analysis.

ing the study. The first, a man 62 years of age, had vasculitis-related aortic-valve involvement and was in remission after six cyclophosphamide pulses (cumulative dose, 4450 mg). At month 8 of azathioprine treatment, he had a major relapse, including recurrent aortic-valve disease, with negative blood cultures and a neutrophil count of 5290 per cubic millimeter. He received methylprednisolone pulses and continued azathioprine treatment, but he died from sepsis 2 weeks later (blood cultures were then positive for *Escherichia coli*). The second patient, a woman 55 years of age, was in remission after nine cyclophosphamide pulses (cumulative dose, 8820 mg). At month 21 of azathioprine treatment, a pancreatic lesion was found on a serial computed tomography scan of the chest and abdomen, along with metastatic liver and vertebral lesions. She started chemotherapy but died 6 months later from cancer progression.

Immunoglobulin Levels, ANCA, and CD19+ B-cell Counts

No significant between-group differences or decreases in total immunoglobulin, IgG, or IgM levels were observed throughout the trial (Fig. S5 in the Supplementary Appendix). Thirteen of the 17 patients in the azathioprine group (76%) who

Table 1. Demographic, Clinical, and Biologic Characteristics of the Patients According to Treatment Group.*

Variable	Azathioprine Group (N=58)	Rituximab Group (N=57)	Total (N=115)	P Value
Age — yr	56±14	54±13	55±13	0.33
Female sex — no. (%)	30 (52)	20 (35)	50 (43)	0.07
ANCA-associated vasculitis type — no. (%)				0.22
Granulomatosis with polyangiitis (Wegener's)	40 (69)	47 (82)	87 (76)	
Microscopic polyangiitis	15 (26)	8 (14)	23 (20)	
Renal-limited ANCA-associated vasculitis	3 (5)	2 (4)	5 (4)	
Disease status — no. (%)				0.78
Newly diagnosed	47 (81)	45 (79)	92 (80)	
Relapsing	11 (19)	12 (21)	23 (20)	
Organ involvement at diagnosis or last flare — no. (%)				
Ear, nose, and throat	41 (71)	48 (84)	89 (77)	0.08
Pulmonary involvement	38 (66)	33 (58)	71 (62)	0.40
Alveolar hemorrhage	11 (19)†	9 (16)	20 (18)†	0.62
Renal involvement	41 (71)	40 (70)	81 (70)	0.95
GFR — ml/min/1.73 m^2				
At disease flare	53.8±35.4	72.0±46.7	62.9±42.3	0.06
At inclusion	59.4±29.7	68.3±29.3	63.9±29.7	0.08
Neurologic involvement — no. (%)	19 (33)	23 (40)	42 (37)	0.40
Cardiac involvement — no. (%)	15 (26)	10 (18)	25 (22)	0.28
Cutaneous involvement, mucosal involvement, or both — no. (%)	22 (38)	20 (35)	42 (37)	0.75
ANCA-positive at diagnosis or last flare — no. (%)				
Indirect immunofluorescence-labeling pattern	54 (93)	54 (95)	108 (94)	0.99
ELISA	53 (91)	53 (93)	106 (92)	0.99
ANCA-positive at inclusion (remission) — no./total no. (%)‡				
Indirect immunofluorescence labeling pattern	39/56 (70)	29/54 (54)	68/110 (62)	0.08
ELISA	23/53 (43)	26/54 (48)	49/107 (46)	0.62
Induction treatment (until remission or randomization) — mg				
Cumulative cyclophosphamide dose	6901±2395	7291±2290†	7095±2341	0.38
Initial daily prednisone dose at diagnosis or flare	64.8±12.9	67.9±13.1	66.3±13.1	0.20
Daily prednisone dose at remission§	16.3±6.6	18.9±7.7	17.6±7.3	0.06

* Plus–minus values are means ±SD. Categorical data were compared with the use of two-by-two tables or Fisher's exact test; continuous data were analyzed with Student's t-test or the Wilcoxon rank-sum test. ANCA denotes antineutrophil cytoplasm antibody, ELISA enzyme-linked immunosorbent assay, and GFR glomerular filtration rate (calculated according to the Modification of the Diet in Renal Disease equation).
† Data were missing for one patient.
‡ Indirect immunofluorescence data were missing for five patients, and ELISA data were missing for eight patients.
§ For details of prednisone use during the trial, see Figure S6 in the Supplementary Appendix.

had major relapses were ANCA-positive at relapse. None of the 3 patients in the rituximab group who had a major relapse, including the 2 who were positive for anti–proteinase 3 ANCA at relapse, had CD19+ B-cell reconstitution at the time of their relapse.

DISCUSSION

In the present study, rituximab was superior to azathioprine at maintaining remission of ANCA-associated vasculitis; this was especially true for granulomatosis with polyangiitis, which was the

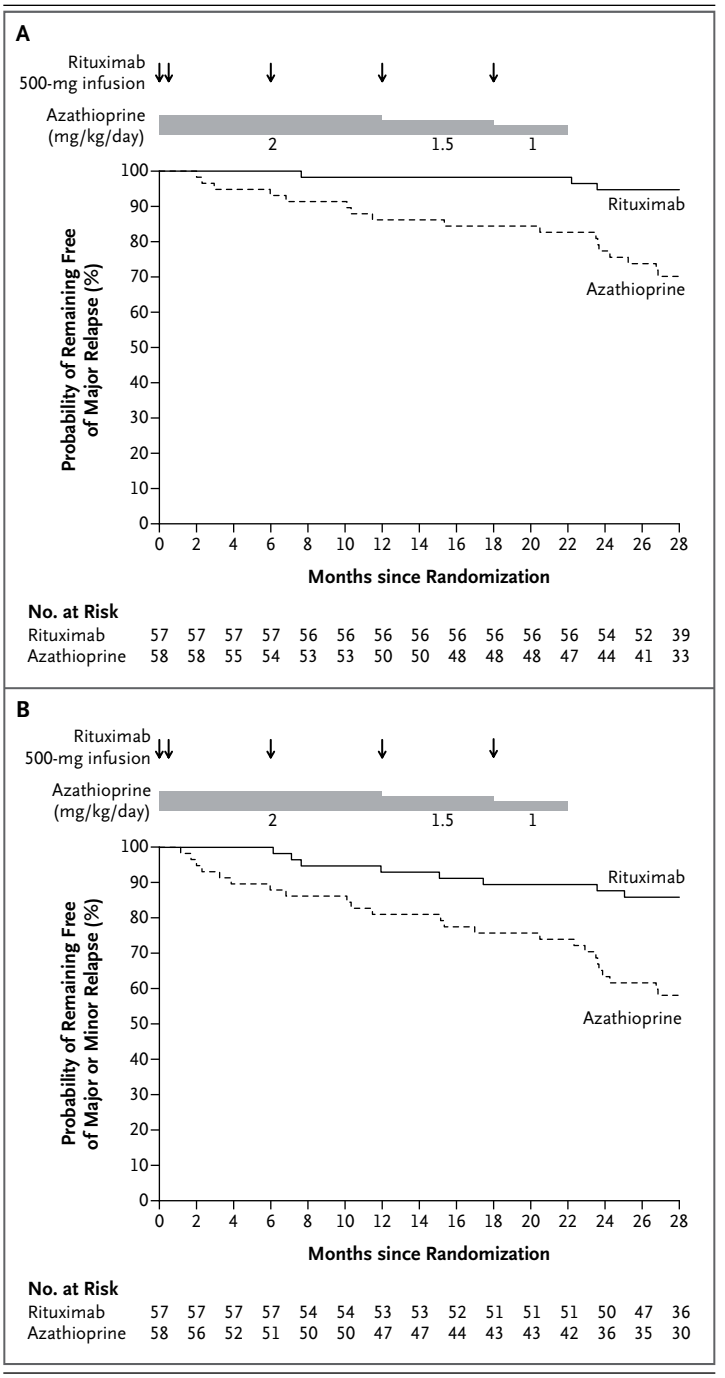

Figure 2. Kaplan–Meier Curves for the Probability of Remaining Free of Relapse According to Treatment Group.

Patients were randomly assigned to receive maintenance therapy with rituximab (500 mg on days 0 and 14 and then months 6, 12, and 18 after the first infusion [arrows]) or azathioprine (2 mg per kilogram per day from month 0 to 12, 1.5 mg per kilogram per day until month 18, then 1 mg per kilogram per day until the last day of month 22 [horizontal gray bars]). Panel A shows the probability of remaining free of major relapse after randomization. The hazard ratio for major relapse for patients in the azathioprine group, as compared with rituximab recipients, was 6.61 (95% CI, 1.56 to 27.96; P=0.002). Panel B shows the probability of remaining free of major or minor relapse after randomization. The hazard ratio for major or minor relapse in patients in the azathioprine group, as compared with rituximab recipients, was 3.53 (95% CI, 1.49 to 8.40; P=0.01).

condition seen in most of the study population. Our data also show that successive 500-mg infusions of rituximab, given every 6 months up to month 18 after remission, were not associated with more frequent severe adverse events than azathioprine.

Although previous studies of ANCA-associated vasculitides identified effective remission-induction treatments,[6,16-18] the best strategy for maintaining remission has been unclear. The present trial was designed to investigate, in patients in remission, the efficacy and safety of systematic rituximab infusions for maintenance, with a 500-mg infusion on days 0 and 14 and then every 6 months. The 6-month interval between infusions was chosen somewhat arbitrarily but was based on reported B-cell reconstitution and relapses after a median of 1 year (range, 4 to 37 months for the latter) in early studies of patients given rituximab for induction.[11,19] The 500-mg rituximab dose is lower than that used for induction or maintenance of remission in other conditions, such as rheumatoid arthritis. We opted for this dose because enrolled patients were in remission — that is, already B-cell–depleted — and with the aim of limiting the risk of infection. We previously treated several patients with the low-dose regimen used in the present study.[20] The results of several recent studies of other autoimmune diseases have also suggested that lower rituximab doses, as compared with the higher ones considered to be conventional, could achieve similar efficacy.[21-24]

Our trial has several strengths. It was designed as a superiority trial to determine whether an expensive therapeutic option (rituximab) would provide a clear advantage over a less costly but not entirely satisfactory option in terms of efficacy and relapse prevention. The 29% rate of major relapse in the azathioprine group was lower than that predicted in our primary hypothesis (40%), which

Table 2. Severe Adverse Events According to Treatment Group.*

Severe Adverse Event	Azathioprine Group (N=58)	Rituximab Group (N=57)
	no. of events	
Infection	8	11
Bronchitis	0	3
Tuberculosis	0	1
Pneumonia with respiratory distress	1	2
Pneumocystis jiroveci pneumonia	0	1
Bacterial endocarditis	1	0
Atypical mycobacterial infection	1	0
Prostatitis	1	0
Herpes zoster infection	1	1
Cholecystitis	1†	0
Septicemia	1‡	0
Esophageal candidiasis	0	1
Infectious diarrhea	1§	2¶
Cancer	2	1
Pancreas	1‡	0
Prostate	0	1
Basocellular carcinoma	1	0
Hematologic event	9	1
Anemia	1	0
Leukopenia	6	0
Lymphopenia	1	1
Thrombocytopenia	1	0
Other‖	25	26

* There were 44 severe adverse events in the azathioprine group and 45 in the rituximab group. A total of 25 patients in each treatment group had at least 1 severe adverse event.
† The patient underwent a cholecystectomy.
‡ The patient died.
§ The infectious diarrhea was caused by *Campylobacter jejuni*.
¶ The infectious diarrhea in one of the patients was caused by *C. jejuni*.
‖ See Table S4 in the Supplementary Appendix for details.

could have masked a difference with rituximab. However, the rate of major relapse in the rituximab group (5%) was also lower than hypothesized, and the observed difference in efficacy reached significance. One possible explanation for these lower relapse rates in both study groups is the long-term use, for at least 18 months after remission, of low-dose prednisone treatment. Although the results of a meta-analysis of several international trials suggested that longer-term, low-dose glucocorticoid use could be associated with fewer relapses, determination of the risks and benefits — especially with regard to infection — of long-term, low-dose prednisone treatment requires further examination in a prospective, controlled study.[25,26]

In the RAVE trial, the induction of remission with rituximab, without any maintenance agent, had no clear safety benefit at 18 months as compared with staged cyclophosphamide–azathioprine treatment.[9] The present maintenance study, involving repeated rituximab infusions or azathioprine treatment, yielded similar rates of adverse events, including infections. Whether the much lower rituximab doses helped to limit the frequencies of adverse events and infections remains unclear. There was no difference between the groups in their plasma total immunoglobulin, IgG, and IgM levels, and changes in these levels did not differ significantly between groups. The persistence of long-lived plasma cells, not affected by rituximab, may have contributed to these findings. The risk of infection in rituximab recipients may depend more on characteristics of the patient and the usually combined glucocorticoid treatment and not only on the cumulative rituximab dose.[27,28] Whereas long-term and repeated rituximab administration appears safe in the treatment of rheumatoid arthritis,[12] such long-term data are not yet available for patients with ANCA-associated vasculitis, who are exposed to more potent immunosuppressive regimens. One patient treated with rituximab had *P. jiroveci* pneumonia develop, which underscores the recommendation that sulfamethoxazole and trimethoprim prophylaxis be used independently of the CD4+ T-lymphocyte count.

The present trial has certain limitations. It was not blinded, and there were fewer patients with antimyeloperoxidase ANCA–positive vasculitis, microscopic polyangiitis, or renal-limited disease than with anti–proteinase 3 ANCA–positive vasculitis or granulomatosis with polyangiitis, thereby potentially limiting the generalizability of our findings to all ANCA vasculitides. Second, prednisone tapering after month 18, when the dose is 5 mg per day or lower, and the decision to discontinue it were left to each site investigator's discretion. However, only 2 of 20 patients with a major relapse had stopped prednisone treatment before the relapse.

By prolonging azathioprine maintenance until month 22, we aimed to compensate for the

likely longer action of rituximab after the last infusion at month 18, thereby limiting possible bias that favored rituximab. However, we also used a gradual tapering scheme for azathioprine between months 12 and 22. Whether azathioprine at such "subtherapeutic" doses is less effective than at higher doses in patients who had been in sustained remission for at least 12 months is unknown. The major-relapse rate after azathioprine dose reduction was not higher than before dose reduction (8 relapses during the first 12 months of treatment and 2 relapses between months 12 and 22), and both were higher than for rituximab recipients. Importantly, several major relapses (7 of 17 in the azathioprine group and 2 of 3 in the rituximab group) occurred after treatment with the trial maintenance drugs was stopped, which is similar to what was observed in previous studies of maintenance.[5,29,30] After only 28 months of follow-up, no firm conclusions can be drawn as to the sustained efficacy of rituximab in the longer term and the reasons for rituximab failure in patients who had a relapse.

In conclusion, the between-group differences in relapse rate observed at month 28 in this trial showed that 500-mg rituximab infusions administered every 6 months were superior to azathioprine as maintenance therapy for ANCA-associated vasculitides, at least for patients positive for anti–proteinase 3 ANCA. Rituximab use for maintenance in those patients was found to have a clear clinical benefit in our study. Further studies are warranted for patients with antimyeloperoxidase ANCA–positive vasculitis.

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APPENDIX

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