Annals of Internal Medicine ORIGINAL RESEARCH

Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial

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Background: Biannual rituximab infusions over 18 months effectively maintain remission after a "standard" remission induction regimen for patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV).

Objective: To evaluate the efficacy of prolonged rituximab therapy in preventing AAV relapses in patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have achieved complete remission after completing an 18-month maintenance regimen.

Design: Randomized controlled trial. (ClinicalTrials.gov: NCT02433522)

Setting: 39 clinical centers in France.

Patients: 68 patients with GPA and 29 with MPA who achieved complete remission after the first phase of maintenance therapy.

Intervention: Rituximab or placebo infusion every 6 months for 18 months (4 infusions).

Measurements: The primary end point was relapse-free survival at month 28. Relapse was defined as new or reappearing symptoms or worsening disease, with a Birmingham Vasculitis Activity Score greater than 0.

Results: From March 2015 to April 2016, 97 patients (mean age, 63.9 years; 35% women) were randomly assigned, 50 to the rituximab and 47 to the placebo group. Relapse-free survival estimates at month 28 were 96% (95% CI, 91% to 100%) and 74% (CI, 63% to 88%) in the rituximab and placebo groups, respectively, an absolute difference of 22% (CI, 9% to 36%) with a hazard ratio of 7.5 (CI, 1.67 to 33.7) ($P = 0.008$). Major relapse–free survival estimates at month 28 were 100% (CI, 93% to 100%) versus 87% (CI, 78% to 97%) ($P = 0.009$), respectively. At least 1 serious adverse event developed in 12 patients (24%) in the rituximab group (with 9 infectious serious adverse events occurring among 6 patients [12%]) versus 14 patients (30%) in the placebo group (with 6 infectious serious adverse events developing among 4 patients [9%]). No deaths occurred in either group.

Limitation: Potential selection bias based on previous rituximab response and tolerance.

Conclusion: Extended therapy with biannual rituximab infusions over 18 months was associated with a lower incidence of AAV relapse compared with standard maintenance therapy.

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The prognosis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has dramatically improved with the advent of glucocorticoid treatment and immunosuppressant or rituximab induction therapy (1). Such regimens lead to remission in 53% to 88% of patients with AAV (2, 3), but relapse rates remain high, making maintenance therapy necessary (4).

Prolonged therapy with azathioprine was once recommended to maintain AAV remission, because a randomized trial showed lower relapse rates with long-term azathioprine therapy compared with the standard-length regimen (5). In 2014, the MAINRITSAN (Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis) trial reported the clear superiority of rituximab over azathioprine in maintaining remission (6), which influenced AAV treatment guidelines (7). The therapeutic schedule of 500 mg of rituximab infused on days 0 and 14, then at months 6, 12, and 18, is now recommended by the U.S. Food and Drug Administration and European Medicines Agency to maintain AAV remission. However, the MAINRITSAN trial showed that relapses after discontinuation of rituximab treatment were frequent, with a 57.9% relapse-free survival rate 32 months after the last rituximab infusion (8).

The MAINRITSAN3 trial was designed to evaluate the efficacy of prolonging the rituximab infusion schedule to maintain remission in patients who achieve com-

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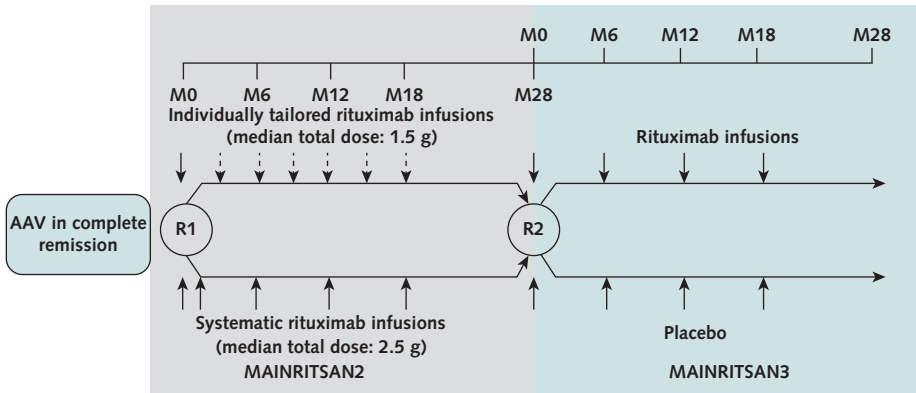
Figure 1. Synopsis of MAINRITSAN2 and MAINRITSAN3.



The primary end point of MAINRITSAN2 was evaluated after 28 mo of follow-up. At that time, eligible patients were randomly assigned again to MAINRITSAN3 treatment groups and evaluated 28 mo later. In MAINRITSAN2, patients in the individually tailored rituximab group received a 500-mg infusion at M0 and subsequent infusions according to laboratory values (ANCA and circulating $CD19^+$ B cells) assessed every 3 mo until M18. Those in the systematic treatment group received a 500-mg infusion on days 0 and 14, then at M6, M12, and M18. In MAINRITSAN3, participants received infusions (500 mg of rituximab or placebo) at inclusion, M6, M12, and M18. AAV = ANCA-associated vasculitis; ANCA = antineutrophil cytoplasmic antibody; M = month; MAINRITSAN = Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis; R = randomization.

plete remission after terminating the first phase of rituximab maintenance therapy (9). Here, we report the results of this new randomized controlled trial comparing the effects of extended maintenance therapy with rituximab versus placebo on prevention of AAV relapses or death.

METHODS

Design Overview

MAINRITSAN3 was a multicenter, double-blind, randomized controlled trial comparing prolonged maintenance therapy with 500-mg rituximab infusions given biannually over 18 months (4 infusions) with placebo (control) (**Figure 1**). Patients were randomly assigned to the 2 groups between March 2015 and April 2016, and follow-up of the last patient ended in August 2018. To be included in the study, patients must have successfully completed the MAINRITSAN2 trial without any major relapses and be in complete remission before being enrolled and reassigned to a group in the MAINRITSAN3 trial.

The MAINRITSAN2 trial compared 2 rituximab infusion strategies (all patients received rituximab) for maintaining remission in patients with AAV: In the individually tailored group, patients received a 500-mg rituximab infusion on day 0 after randomization, with reinfusion only if $CD19^+$ B lymphocytes or ANCAs reappeared, or if the ANCA titer rose markedly. In the control group, patients received a fixed 500-mg rituximab infusion on day 0 after randomization, then at months 6, 12, and 18. The primary end point was evaluated at month 28; at that time, participants' eligibility for MAINRITSAN3 was determined.

Le Comité de Protection des Personnes (Île-de-France 1 [Paris]) approved the study (EudraCT: 2012-001963-66; Am6505-7-2988), which received legal, monitoring, and administrative support from Assistance Publique–Hôpitaux de Paris.

Setting and Participants

Patients were recruited from 39 French centers (academic medical centers and community hospitals). Eligible patients had granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), as defined by the Chapel Hill Consensus Conference nomenclature (10); must have completed the MAINRITSAN2 trial (9); and must have been in complete remission at the time of rerandomization.

Complete remission was defined as a Birmingham Vasculitis Activity Score (BVAS; version 3) of 0 (score range, 0 to 63, with higher scores indicating more active disease) (11). Patients who had a minor relapse treated only with an increased glucocorticoid dose and who had achieved remission at the end of the MAINRITSAN2 trial were eligible for inclusion in MAINRITSAN3. MAINRITSAN2 participants who had a major relapse were not eligible for MAINRITSAN3. Complete inclusion and exclusion criteria for MAINRITSAN2 are presented in **Supplement 1**. All patients provided written informed consent.

Randomization and Interventions

Patients were randomly assigned in a 1:1 ratio to receive prolonged maintenance therapy with rituximab or placebo. An independent statistician provided the computer-generated, random-permuted, block randomization sequence, stratified by MAINRITSAN2 randomization group (individually tailored or systematic) and whether AAV was newly diagnosed or relapsing (that is, relapsed at least once since first remission) at the time of MAINRITSAN2 enrollment. Randomization was centralized through the electronic case report form to ensure allocation concealment.

Patients received an intravenous 500-mg fixed dose of rituximab or placebo at randomization and at months 6, 12, and 18. Rituximab and placebo were reconstituted by designated pharmacy personnel who were aware of the study group assignments. These persons had no contact with patients and were not involved in any clinical aspects of the study, including rituximab or placebo infusion, clinical evaluations, and assessment of adverse events.

Patients received premedication with intravenous methylprednisolone (100 mg), dexchlorpheniramine (5 mg), and acetaminophen (1000 mg) before all rituximab and placebo infusions. Many patients were still receiving low-dose prednisone at randomization; this therapy was tapered and was either stopped or maintained at 5 mg/d, at the discretion of each site investigator. *Pneumocystis jirovecii* pneumonia prophylaxis was recommended for all patients (daily sulfamethoxazole–trimethoprim [400/80 mg], or monthly pentamidine aerosolizations for patients with sulfa drug allergy).

Outcomes and Follow-up

The primary end point was relapse-free survival 28 months after MAINRITSAN3 randomization. Relapse was defined as reappearance or worsening of AAV symptoms, that is, BVAS greater than 0. Secondary end points included major and minor relapse–free survival. Major relapse was defined as life threatening or involving at least 1 major organ, minor relapse as AAV reappearance or worsening, with BVAS greater than 0, not corresponding to a major relapse.

Other secondary end points included damage as evaluated with the Vasculitis Damage Index, health-related quality of life, potential association of ANCA evolution or $CD19^+$ B-cell counts with relapses, cumulated glucocorticoid dose, serum γ-globulin levels, and death. We also recorded all adverse events, treatment related or not. Health-related quality of life was assessed with the Physical Functioning Scale and Mental Health Component scores of the Medical Outcomes Study 36-Item Short-Form Health Survey (12) and the Health Assessment Questionnaire.

Study visits were scheduled at randomization, then every 3 months until the end of the study, 28 months after randomization. Patients who discontinued treatment remained under follow-up until month 28. At each visit, BVAS was calculated and blood samples were drawn from every patient for analysis, which included ANCA titers and circulating $CD19^+$ B-cell counts. Patients were asked to record their study medication weekly in a specifically designated diary. To prevent unblinding due to the observation of rituximab-induced B-cell depletion, all trial personnel were unaware of patients' $CD19^+$ B-cell counts. An independent laboratory assessor was designated to monitor and collect those results.

An independent adjudication committee including 3 vasculitis experts (X. Puéchal, O. Lidove, and M. Gayraud), who were blinded to study group assignments and circulating $CD19^+$ B-cell counts, evaluated all relapses on the basis of the electronic case report forms and prepared medical files. A member of the clinical research unit (A. Clabaux) collected the medical files of patients who had had a relapse according to the investigators; anonymized them; and prevented the assigned randomization group from being revealed, especially for patients who had a major relapse and discontinued treatment. The adjudication committee met twice (July 2018 and January 2019) in the presence of P. Charles and clinical research unit members A. Berton and A. Bruneau. If the diagnosis of relapse was not retained, the BVAS was corrected to 0. If a relapse could not be confirmed by the medical files, the committee telephoned the investigator treating the patient to obtain a more detailed description of the potential relapse and the event was reassessed.

Statistical Analysis

The trial was designed to detect, with 80% power, a 20% absolute difference in the between-group incidences of death or relapse at month 28, assuming a 30% incidence for the control group and using a 2-sided test and an α-level of 0.05. On the basis of those assumptions, 59 patients per group were needed. No allowance for missing data was incorporated into the sample size calculation.

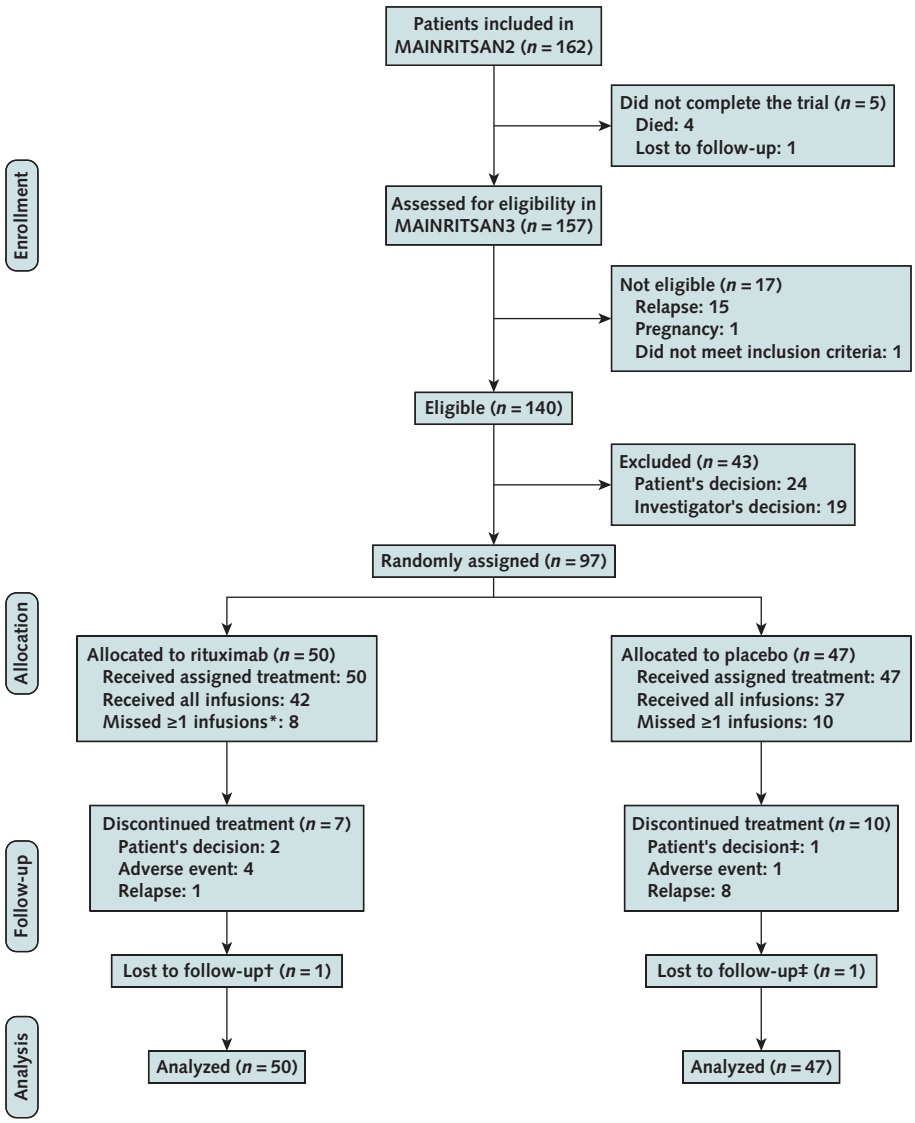
The statistical analyses were conducted according to the intention-to-treat principle, including all patients in their randomly assigned group. For descriptive analyses, qualitative variables are expressed as number (percentage) and quantitative variables as mean (SD) or median (interquartile range [IQR]), as appropriate. Relapse-free survival percentages were estimated by using the Kaplan–Meier method. Patients who completed the study without a relapse were censored at month 28 after MAINRITSAN3 randomization. The absolute difference between the relapse-free survival percentages at month 28 was calculated with bootstrap 95% CIs. A Cox model, adjusted for disease flare category (newly diagnosed or relapsing AAV) at MAINRITSAN2 enrollment and for MAINRITSAN2 randomization group, was used to compare the instantaneous risk for relapse or death between the rituximab and placebo groups. The results are expressed as hazard ratios with 95% CIs. A sensitivity analysis consisted of an unadjusted analysis. According to the Grambsch and Therneau test, the proportional hazards assumption of the Cox model was reasonable with a P value of 0.55. The approaches used to account for missing data were prespecified. For the primary end point, patients who exited the trial before relapse were censored at their last visit. Statistical analysis methods for secondary end points are given in **Supplement 1**.

Statistical analyses were computed with R, version 3.4.4 (R Foundation for Statistical Computing). We used the *coxph* function from the survival package for survival analyses, the *lmer* function from the lme4 package for longitudinal analyses, the *bootkm* function from the Hmisc package for the bootstrap, and the *glm* function for the Poisson model.

Role of the Funding Source

The trial was sponsored by the Assistance Publique–Hôpitaux de Paris and funded by the Programme Hospitalier de Recherche Clinique of the

Figure 2. Flow chart of the study.



Patients who discontinued treatment remained under follow-up until month 28. MAINRITSAN = Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis.
* One patient temporarily stopped treatment.
† Patient was lost to follow-up after receiving all the infusions.
‡ Patient discontinued treatment and was lost to follow-up.

French Ministry of Health (PHRC National 2011 AOM11145) and a research grant from Hoffmann–La Roche, which also provided rituximab for the study. Hoffmann–La Roche was not involved in the study design and did not have access to the data.

RESULTS

Patient Characteristics

In MAINRITSAN2, 162 patients were randomly assigned to a study group: 157 completed the trial and, at the last evaluation, 140 were eligible for rerandomization in MAINRITSAN3 (**Figure 2**). Of these patients, 24 declined participation and 19 were not included by their treating physicians. Further information is given in **Supplement 1**.

Ninety-seven patients were randomly assigned, 68 (70%) with GPA and 29 (30%) with MPA; 57 (59%) had newly diagnosed AAV and 40 (41%) relapsing disease. Fifty patients (52%) were assigned to receive rituximab and 47 (48%) placebo. Characteristics of patients in both groups were similar (**Table 1**). Forty-two patients in the rituximab group received all the infusions, and 8 discontinued treatment. Thirty-seven patients in the placebo group received all the infusions, and 10 discontinued treatment. One patient in each treatment group was lost to follow-up before month 28.

Primary End Point

Relapse-free survival at 28 months was 96% (95% CI, 91% to 100%) in the rituximab group versus 74% (CI, 63% to 88%) in the placebo group, an absolute difference of 22% (CI, 9% to 36%); the hazard ratio was 7.5 (CI, 1.67 to 33.7) (P = 0.008) (Figure 3, *top*).

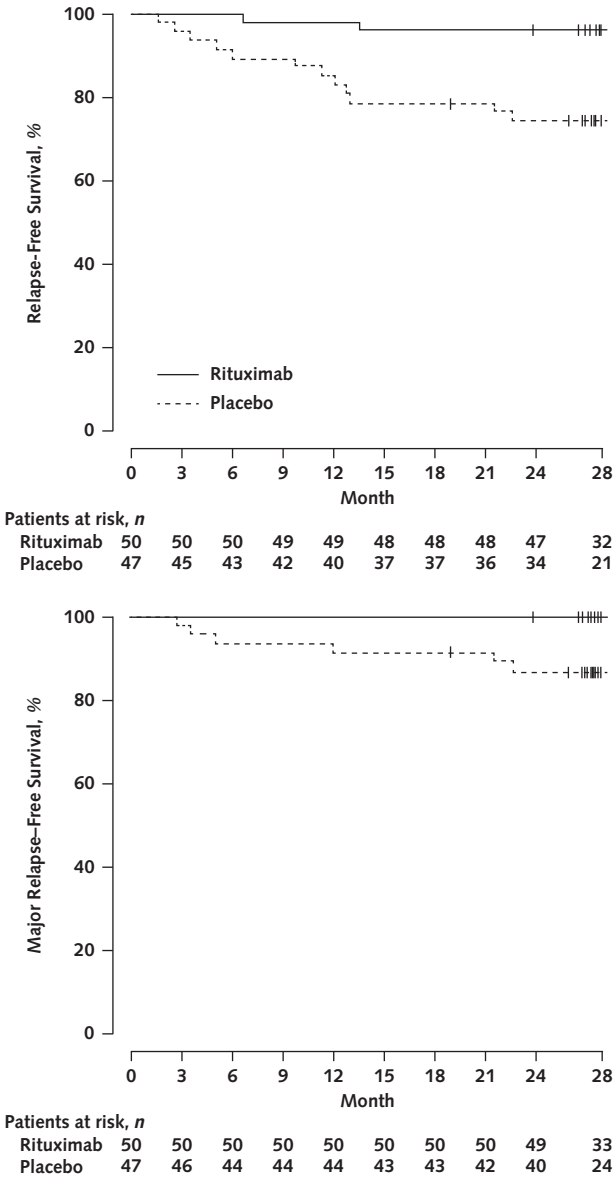
No patient died during the study. Relapse occurred in 2 patients in the rituximab group. One of the pa-

Table 1. General Characteristics at Inclusion*

Characteristic	Rituximab Group (n = 50)	Placebo Group (n = 47)
Mean age (SD), *y*	64.6 (10.7)	63.1 (11.2)
Female	15 (30)	19 (40)
Vasculitis type		
GPA	32 (64)	36 (77)
MPA	18 (36)	11 (23)
Disease status		
At MAINRITSAN2 inclusion		
Newly diagnosed	32 (64)	31 (66)
Relapsing	18 (36)	16 (34)
At MAINRITSAN3 inclusion		
Newly diagnosed	27 (54)	30 (64)
Relapsing	23 (46)	17 (36)
MAINRITSAN2 randomization group		
Individually tailored rituximab infusions	24 (48)	22 (47)
Systematic rituximab infusions	26 (52)	25 (53)
Induction treatment of last disease flare		
Cyclophosphamide	31 (62)	31 (66)
Rituximab	18 (36)	16 (34)
Methotrexate	1 (2)	0 (0)
Prednisone	26 (52)	29 (62)
Median dose (IQR), *mg*	5 (5–5)	5 (5–5)
Organ involvement at initial disease for "newly diagnosed" or at last relapse requiring immunosuppressants or rituximab		
Ear, nose, and throat	21 (42)	25 (53)
Pulmonary	19 (38)	20 (43)
Renal	31 (62)	30 (64)
Mean eGFR at inclusion (SD), *mL/min/1.73 m²*	55 (25)	64 (22)
ANCA-positive results		
At diagnosis or last relapse†	47 (98)	47 (100)
Indirect immunofluorescence	43 (90)	42 (89)
ELISA	39 (81)	42 (89)
Anti-PR3	23 (48)	25 (53)
Anti-MPO	16 (33)	17 (36)
At inclusion‡	27 (54)	21 (46)
Indirect immunofluorescence	25 (50)	19 (41)
ELISA	18 (36)	15 (33)
Anti-PR3	6 (12)	7 (15)
Anti-MPO	12 (24)	8 (17)
γ-Globulin		
Mean level (SD), *g/L*	7.0 (2.0)	7.0 (2.2)
Patients with levels <4 g/L§	3 (6)	1/46 (22)
Patients with levels <5 g/L§	7 (15)	9/46 (20)
Mean immunoglobulin (SD) level, *g/L*		
IgG	7.11 (2.12)	7.24 (2.16)
IgM	0.44 (0.28)	0.36 (0.2)

ANCA = antineutrophil cytoplasmic antibody; eGFR = estimated glomerular filtration rate; ELISA = enzyme-linked immunosorbent assay; GPA = granulomatosis with polyangiitis; IQR = interquartile range; MAINRITSAN = Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase-3.
* Values are numbers (percentages) unless otherwise indicated.
† Data missing for 2 patients in the rituximab group.
‡ Data missing for 1 patient in the placebo group.
§ Data missing for 3 patients in the rituximab group and 1 patient in the placebo group.

Figure 3. Kaplan–Meier estimates of relapse-free survival (*top*) and major relapse–free survival (*bottom*), according to treatment group.



tients, who had MPA and antimyeloperoxidase (anti-MPO) ANCAs, developed febrile neutropenia 3 months after randomization and rituximab infusion, discontinued treatment, and had a relapse at month 14. The other patient, who had GPA and anti–proteinase-3 (PR3) ANCAs, had a relapse at month 7, 1 month after the last rituximab infusion. Among the 12 patients in the placebo group who had a relapse, 10 (83%) had GPA and 2 (17%) had MPA, 6 were having their first relapse, 10 had anti-PR3 positivity, and 2 had anti-MPO ANCA positivity. During MAINRITSAN2, 5 of the 12 patients received individually tailored rituximab infusions and 7 received systematic infusions. Median time to relapse in the placebo group was 22 months (IQR, 20 to 23 months) after the last MAINRITSAN2 rituximab infusion. Relapses are described in detail in Tables 1 and 2 of Supplement 1 (available at Annals.org).

Secondary End Points

Major and Minor Relapses

Major relapse–free survival was 100% (CI, 93% to 100%) in the rituximab group versus 87% (CI, 78% to 97%) in the placebo group ($P = 0.009$) (Figure 3, *bottom*). Six patients in the placebo group had major relapses: 3 renal and 3 pulmonary flares (alveolar hemorrhage, bronchial stenosis, or nodules). All patients received a new induction regimen with high-dose glucocorticoids and rituximab, and all subsequently achieved remission. One patient had permanently impaired renal function but did not require extrarenal dialysis.

Minor relapse–free survival was 96% (CI, 91% to 100%) in the rituximab group versus 87% (CI, 78% to 97%) in the placebo group ($P = 0.134$).

Damage and Quality of Life

Mean Vasculitis Damage Index scores for the rituximab and placebo groups, respectively, were 2.2 (SD, 1.9) and 1.6 (SD, 1.6) at inclusion and 2.2 (SD, 1.8) and 1.7 (SD, 1.6) at month 28. The 2 groups did not differ significantly at the end of the trial (difference in mean change from baseline, 0.00 [CI, −0.12 to 0.11]; $P = 0.95$). Quality-of-life outcomes also did not differ significantly over the course of the study between the 2 groups (Tables 3 to 5 of Supplement 1, available at Annals.org).

AAV Relapses Related to ANCA and B-Cell Repopulation

Five ANCA evolution profiles were identified (Table 6 of Supplement 1, available at Annals.org). At month 28, 14 of 47 patients (30%) in the rituximab group had ANCA positivity, versus 24 of 43 patients (56%) in the placebo group ($P = 0.057$). Of note, the ANCA evolution pattern of "negative at inclusion but becoming positive" seemed to be associated with AAV flares: It was observed in 50% of patients who had a relapse versus 15% of those who did not. Only 1 patient with persistent ANCA negativity had a relapse. No patients with ANCA and $CD19^+$ B-cell negativity had a relapse. In the placebo group, 10 of 25 patients (40%) with PR3 ANCA positivity had a relapse, versus 2 of 17 patients (12%) with MPO ANCA positivity.

Glucocorticoid Use

Cumulative mean glucocorticoid doses after randomization did not differ significantly between the rituximab (2565 mg [SD, 2932]) and placebo (3376 mg [SD, 3371]) groups ($P = 0.22$). At the end of the trial, 19 of 49 patients (39%) in the rituximab group were still receiving glucocorticoids, versus 23 of 46 patients (50%) in the placebo group (data are missing for 2 patients, 1 in each group, who were not receiving glucocorticoids at their last visit). For patients in the rituximab

and placebo groups receiving prednisone at the end of the trial, the respective median doses were 5 mg (IQR, 5 to 5 mg) and 5 mg (IQR, 5 to 8.75 mg).

Safety

Forty-six patients (92%) in the rituximab group and 44 (94%) in the placebo group had at least 1 adverse event ($P = 0.68$), with 12 (24%) and 14 (30%), respectively, having at least 1 serious adverse event ($P = 0.65$), for a total of 21 and 18 serious adverse events per group, respectively (**Table 2**; and **Table 7** of **Supplement 1**, available at Annals.org).

Nine infectious serious adverse events occurred among 6 patients (12%) in the rituximab group (2 cases each of septic shock and urinary tract infection and 1 case each of Lyme disease, acute cholangitis, neutropenia, bronchitis, and pneumonia), whereas 6 events occurred among 4 patients (9%) in the placebo group (4 cases of pneumonia, 1 case of influenza, and 1 *P jirovecii* infection in a patient receiving methotrexate and glucocorticoids for a relapse that occurred after treatment discontinuation).

Mean γ-globulin levels at the end of the study were 6.6 g/L (SD, 1.9) in the rituximab group and 7.9 g/L (SD, 2.9) in the placebo group ($P < 0.001$) (**Figure** in **Supplement 1**, available at Annals.org). At the end of the trial, the numbers of patients in the rituximab and placebo groups, respectively, who had hypogammaglobulinemia were 2 of 48 (4%) and 3 of 43 (7%) for a threshold of less than 4 g/L, and 10 of 48 (21%) and 6 of 43 (14%) for a threshold of less than 5 g/L (**Table 8** of **Supplement 1**, available at Annals.org). At the last determination, mean IgG and IgM levels, respectively, were 6.60 g/L (SD, 1.97) and 0.44 g/L (SD, 0.37) in the rituximab group versus 8.02 g/L (SD, 2.92) and 0.48 g/L (SD, 0.43) in the placebo group.

DISCUSSION

In the MAINRITSAN3 trial, we compared a long-term rituximab maintenance regimen with placebo by using the MAINRITSAN-defined rituximab regimen (6), which is now recommended for maintaining remission from AAV. Our results demonstrated that prolonging rituximab treatment—that is, with 500 mg infused every 6 months for an additional 18 months after an initial 18-month maintenance regimen—was effective in sustaining remission, with relapse occurring in only 2 of 50 patients (4% [CI, 0% to 9%]) in the rituximab group versus 12 of 47 (26% [CI, 12% to 37%]) in the placebo group during the 28-month follow-up. No deaths occurred in either group. Long-term rituximab maintenance therapy did not seem to increase the number of adverse events or their severity. The incidence of serious infection in the rituximab group was 12%, which was not higher than that of the placebo group and was lower than that observed in other randomized controlled trials (6, 9) and observational studies (13, 14) assessing rituximab, possibly because MAINRITSAN3 participants had already received rituximab and tolerated it well. The difference also might be explained by patients having had their last flares (when they had received high doses of immunosuppressants and glucocorticoids) long before they were enrolled in the current trial (median, 33 months [IQR, 32 to 35 months]).

In this study, relapses seemed to occur more frequently in patients with AAV and PR3 ANCA positivity than in those with MPO positivity. These findings are consistent with other data (8, 15–18) and suggest that long-term rituximab administration may be beneficial and might be a therapeutic option for this subpopulation of patients. MAINRITSAN3 adds another piece to the puzzle of the ability of ANCA titers and circulating $CD19^+$ B-cell counts to predict relapses (9, 14, 19, 20). We did not find a strong association between those parameters and relapses; however, of note, 7 of 12 patients (58%) in the placebo group who had a relapse initially had ANCA negativity and then developed positivity. As in the RAVE (Rituximab for ANCA-Associated Vasculitis) study follow-up, no patient with ANCA and circulating $CD19^+$ B-cell negativity had a relapse (14).

This study had some limitations. The main limitation was the potential risk of selection bias, because the study included only patients in complete remission with rituximab who had no severe adverse events after the first MAINRITSAN2 maintenance phase. Also, the trial enrolled fewer patients than expected, although it did have sufficient power to demonstrate rituximab superiority. Recruitment to MAINRITSAN3 was difficult, because to be eligible, patients must have completed MAINRITSAN2 and been willing to participate in this new randomized trial, possibly receiving the placebo, with a visit every 3 months. Nonetheless, 97 of 140 eligible patients (69%) were enrolled in this second randomized controlled trial, providing a total of 56 months

Table 2. Adverse Events, According to Treatment Group*

Event	Rituximab Group ($n = 50$)	Placebo Group ($n = 47$)
Death	0	0
Patients reporting AEs		
Any AE	46 (92)	44 (94)
AE leading to discontinuation of therapy	4 (8)	1 (2)
Serious AE	12 (24)	14 (30)
Infectious serious AE	6 (12)	4 (9)
Serious AEs	21	18
Infectious	9	6
Septic shock	2	0
Pneumonia	1	4
Pneumocystis jirovecii infection	0	1
Prostatitis	1	0
Pyelonephritis	1	0
Lyme meningitis	1	0
Acute cholangitis (gallstones)	1	0
Febrile neutropenia	1	0
Bronchitis	1	0
Influenza	0	1
Thromboembolic	2	1
Cardiac	1	1
Other	9	10

AE = adverse event.
* Values are numbers (percentages).

of follow-up, which is the longest trial of AAV monitoring to our knowledge. This high percentage also demonstrates the motivation of patients and treating physicians. Another limitation was that biological parameters were assayed at each participating center. However, all ANCA titers and $CD19^+$ B-cell counts for an individual patient had to be assayed in the same laboratory.

The 3 MAINRITSAN trials have provided many insights into AAV: Rituximab should become the new gold standard to maintain remission, a 500-mg dose per infusion is sufficient, treatment should be prolonged, and an individually tailored regimen may be prescribed. On the basis of our results, we propose that future rituximab use be prolonged for patients at high risk for relapses, such as those with PR3 ANCAs and those who have already had a relapse.

In conclusion, extended biannual rituximab infusions for an additional 18 months achieved a lower incidence of AAV relapse compared with standard 18-month maintenance therapy. No patients died in either treatment group.

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Correction: This article was corrected on 9 July 2020 to correct information about the infusion strategy in the rituximab group.

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