

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 15, 2010

VOL. 363 NO. 3

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

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ABSTRACT

BACKGROUND

Cyclophosphamide induction regimens for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are effective in 70 to 90% of patients, but they are associated with high rates of death and adverse events. Treatment with rituximab has led to remission rates of 80 to 90% among patients with refractory ANCA-associated vasculitis and may be safer than cyclophosphamide regimens.

METHODS

We compared rituximab with cyclophosphamide as induction therapy in ANCA-associated vasculitis. We randomly assigned, in a 3:1 ratio, 44 patients with newly diagnosed ANCA-associated vasculitis and renal involvement to a standard glucocorticoid regimen plus either rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks, with two intravenous cyclophosphamide pulses (33 patients, the rituximab group), or intravenous cyclophosphamide for 3 to 6 months followed by azathioprine (11 patients, the control group). Primary end points were sustained remission rates at 12 months and severe adverse events.

RESULTS

The median age was 68 years, and the glomerular filtration rate (GFR) was 18 ml per minute per 1.73 m² of body-surface area. A total of 25 patients in the rituximab group (76%) and 9 patients in the control group (82%) had a sustained remission ($P=0.68$). Severe adverse events occurred in 14 patients in the rituximab group (42%) and 4 patients in the control group (36%) ($P=0.77$). Six of the 33 patients in the rituximab group (18%) and 2 of the 11 patients in the control group (18%) died ($P=1.00$). The median increase in the GFR between 0 and 12 months was 19 ml per minute in the rituximab group and 15 ml per minute in the control group ($P=0.14$).

CONCLUSIONS

A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events. (Funded by Cambridge University Hospitals National Health Service Foundation Trust and F. Hoffmann–La Roche; Current Controlled Trials number, ISRCTN28528813.)

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N Engl J Med 2010;363:211-20.

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ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)-associated vasculitis, including Wegener's granulomatosis and microscopic polyangiitis, is a multisystem autoimmune syndrome characterized by vasculitis predominantly affecting microscopic vessels and circulating autoantibodies to neutrophil cytoplasmic antigens. Renal involvement occurs in 70% of affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy. The current standard of care for ANCA-associated vasculitis is cyclophosphamide with high-dose glucocorticoids¹⁻⁴; such regimens are effective in 70 to 90% of patients. However, cyclophosphamide is associated with leukopenia, severe infections, cancer, and ovarian failure.⁵ Mortality at 1 year exceeds 15%; infection and active vasculitis are the predominant causes of early death. The partial efficacy and severe toxicity of such regimens indicate a need for better induction therapy in ANCA-associated vasculitis.

Rituximab is a B-cell-depleting anti-CD20 monoclonal antibody that has been approved by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of non-Hodgkin's lymphoma⁶ and rheumatoid arthritis.⁷⁻¹⁰ In ANCA-associated vasculitis, B-cell activation and levels of B-cell-activating factor correlate with disease activity.^{11,12} CD20-positive, B-cell-rich, follicle-like areas containing autoreactive memory B cells with affinity for the ANCA antigen, proteinase 3, are present in Wegener's granulomas.^{13,14} ANCAs are implicated in the pathogenesis of ANCA-associated vasculitis.¹⁵ Furthermore, cyclophosphamide suppresses the activation, proliferation, and differentiation of autoreactive B cells.¹⁶ These findings of a pathogenic role of B cells and ANCAs in ANCA-associated vasculitis provide support for the use of a B-cell-targeted therapy.

Sustained remissions have been reported in 80 to 90% of patients with refractory ANCA-associated vasculitis who were treated with rituximab.¹⁷⁻²³ We conducted a randomized trial of rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS). The purpose of the trial was to assess the treatment response and rates of associated severe adverse events with a rituximab-based regimen, as compared with a cyclophosphamide-based regimen, as induction

therapy in patients with recently diagnosed, severe ANCA-associated vasculitis, in the hope that a rituximab-based regimen might be more effective and safer. A related article on the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (ClinicalTrials.gov number, NCT00104299), which compared rituximab with standard cytotoxic therapy for the induction of complete remission by 6 months in patients with severe ANCA-associated vasculitis, is reported elsewhere in this issue of the *Journal*.²⁴

METHODS

STUDY DESIGN AND PATIENTS

The study was an open-label, two-group, parallel-design, randomized trial involving 44 patients from eight centers in Europe and Australia. All patients provided written informed consent.

Inclusion in the study required a new diagnosis of ANCA-associated vasculitis,^{25,26} ANCA positivity, and renal involvement, as evidenced by necrotizing glomerulonephritis on biopsy or red-cell casts or hematuria (≥ 30 red cells per high-power field) on urinalysis. The trial protocol is available with the full text of this article at NEJM.org and at www.vasculitis.org.

Randomization was performed with the use of a computer minimization algorithm to maintain concealment of study-group assignments from the investigators. This algorithm was stratified according to the patients' age, diagnosis, and baseline renal function (see details in the Supplementary Appendix, available at NEJM.org). A 3:1 ratio for random assignment was used in view of our extensive previous experience with the control regimen² and a greater need to characterize the safety of rituximab.

The trial was sponsored by Cambridge University Hospitals National Health Service Foundation Trust. F. Hoffmann–La Roche provided the rituximab and a research grant that contributed to trial costs. The trial, which was designed by the first and last authors and the trial steering committee, received ethical approval from the ethics committee of each participating center and was conducted according to the European Union Clinical Trials Directive (Directive 2001 EU/20/EC),²⁷ (EudraCT number, 2005-003610-15). Regulatory approval was obtained from the national regulatory authorities in each country. The

data were held by the investigators at Addenbrooke's Hospital. All of the authors decided to submit the manuscript for publication.

TREATMENTS

Before enrollment, patients were allowed to undergo plasma exchange or to receive a maximum of 2 g of intravenous methylprednisolone, according to local practice for managing severe disease. After randomization, the two groups received intravenous methylprednisolone (at a dose of 1 g) and the same oral glucocorticoid regimen (1 mg per kilogram per day initially, with a reduction to 5 mg per day at the end of 6 months). Patients in the rituximab group received rituximab (MabThera, Roche) at a dose of 375 mg per square meter per week, for 4 consecutive weeks, and intravenous cyclophosphamide at a dose of 15 mg per kilogram with the first and third rituximab infusions; these patients did not receive azathioprine to maintain remission. For patients in the rituximab group who had progressive disease within the first 6 months, a third dose of intravenous cyclophosphamide (at a dose of 15 mg per kilogram) was permitted. Patients in the control group received a validated regimen of intravenous cyclophosphamide for 3 to 6 months, followed by azathioprine (see the Supplementary Appendix).^{2,3} Further treatment with rituximab or cyclophosphamide was permitted in cases of relapse. Relapses occurring before a minimum of 6 months of sustained remission were considered failures with respect to the primary efficacy end point.

ASSESSMENTS

Assessments were performed at 0, 1.5, 3, 6, 9, and 12 months and at the time of a relapse (Supplementary Appendix). Remission was defined as an absence of clinical disease activity, as indicated by a Birmingham Vasculitis Activity Score (BVAS)²⁸ of 0 that was maintained for 2 months (scores range from 0 to 63, with higher scores indicating more active disease). Sustained remission was defined as an absence of disease activity (BVAS of 0) for at least 6 months. Relapse was defined as the recurrence or new appearance of any disease activity, as reflected by the BVAS, that was attributable to active vasculitis (Supplementary Appendix). Progressive disease was defined as either the persistence of hematuria and proteinuria, with an absence of improvement in the glomerular filtration

rate (GFR),²⁹ or the continuation of a major non-renal item, as indicated by the BVAS, at 6 weeks.

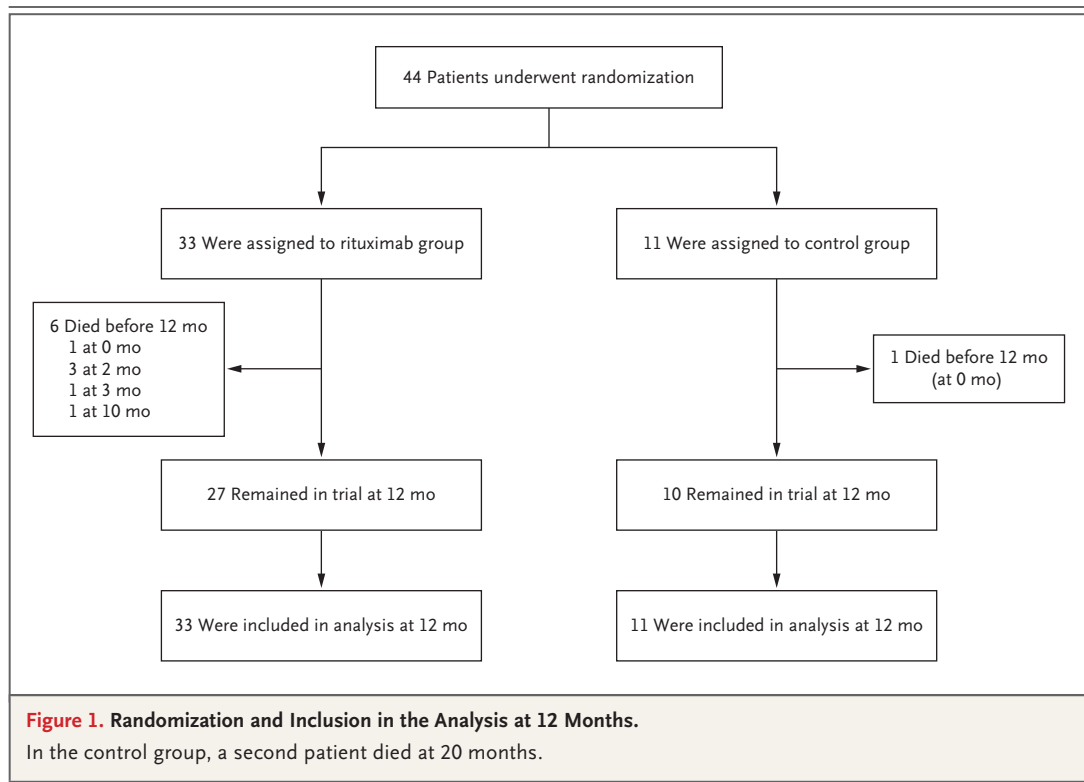
OUTCOMES

Outcomes were adjudicated by three investigators and by an independent assessor who was unaware of the study-group assignments. The primary outcomes were sustained remission and rates of severe adverse events²⁷ at 12 months. Deaths and malignant conditions occurring after 12 months were also recorded. Secondary efficacy end points were time to remission, change in the BVAS between 0 and 3 months, change in the GFR, prednisolone dose, score on the Medical Outcomes Study 36-Item Short Form (SF-36) questionnaire,³⁰ and score on the Vasculitis Damage Index (scores for this index range from 0 to 64, with higher scores indicating more severe damage)³¹ between 0 and 12 months. Secondary safety end points were serious adverse events, infections, and death.

STATISTICAL ANALYSIS

We anticipated a sustained-remission rate of 95% among patients in the rituximab group.¹⁹ Among patients in the control group, we expected a remission rate of 80% and a sustained-remission rate of 65% because of early relapses. We estimated that with 44 patients undergoing randomization, the study would have a statistical power of more than 80%, at a two-sided alpha level of 0.05. The smallest difference in risk that our trial was powered to detect was a 33% increase (95% confidence interval [CI], 4 to 63) in the rate of sustained remission, corresponding to a risk ratio of 1.5. This difference was considered clinically important.

Analyses were performed on an intention-to-treat basis. All analyses included 44 patients. Missing laboratory data (e.g., the GFR) for patients who died were imputed with the use of the last-value-carried-forward method to provide a conservative estimate of effects. Results are expressed as values and percentages for categorical variables and medians and interquartile ranges for continuous variables (mean values are provided in the Supplementary Appendix). Proportions were compared with the use of the chi-square test. Adverse events are expressed as incidence rates. Time-to-event analyses were performed with the use of the log-rank test. Analysis of covariance was used to assess the change in the GFR.³² P values of less than 0.05 were considered to indicate statis-



tical significance. All statistical tests were two-sided. All analyses were performed with the use of Stata software, version 10.

RESULTS

PATIENTS

Between June 2006 and June 2007, a total of 44 patients were enrolled in the study (33 in the rituximab group and 11 in the control group). No patients were lost to follow-up. Six patients in the rituximab group and 1 patient in the control group had died by 12 months (Fig. 1). An additional patient in the control group died at 19 months. Characteristics of the patients are shown in Table 1. The median age at study entry was 68 years. The use of plasma exchange was balanced between the groups (Table 1). Two patients in the rituximab group received a third dose of cyclophosphamide: one was classified as having a treatment failure; the other, who had a response to the rituximab regimen and received the third cyclophosphamide dose in violation of the protocol, was classified as having successful treatment.

PRIMARY OUTCOMES

Sustained Remission

Sustained remission occurred in 25 of 33 patients in the rituximab group (76%) and 9 of 11 patients in the control group (82%). The absolute difference in sustained remission with rituximab as compared with cyclophosphamide was −6 percentage points (95% CI, −33 to 21; $P=0.68$). Six patients in the rituximab group and 1 patient in the control group died within the first 12 months. Among the patients who survived, 93% of the patients in the rituximab group and 90% of the patients in the control group had sustained remission ($P=0.80$). In addition to the 7 patients who died, 3 patients did not have a sustained remission: 1 patient in the rituximab group who received rituximab retreatment for incomplete remission at 5 months (which subsequently led to full remission) and 2 patients, 1 in each treatment group, who had a relapse within 6 months after remission had been achieved. Among the 9 patients who were dependent on dialysis at study entry, 6 of the 8 patients in the rituximab group had a sustained remission (5 of whom

no longer required dialysis), and the 1 patient in the control group died shortly after study entry.

The median time to remission was 90 days (interquartile range, 79 to 112) in the rituximab group and 94 days (interquartile range, 91 to 100) in the control group ($P=0.87$) (Fig. 2A).

Adverse Events

A total of 31 severe adverse events occurred in 14 of the 33 patients in the rituximab group (42%) and 12 severe adverse events occurred in 4 of the 11 patients in the control group (36%) (Table 2). Incidence rates for severe adverse events were 1.00 per patient-year in the rituximab group (95% CI, 0.69 to 1.44) and 1.10 per patient-year in the control group (95% CI, 0.61 to 1.99; $P=0.77$) (Fig. 2B).

A total of 19 infections occurred in 12 of the 33 patients in the rituximab group (36%), and 7 infections occurred in 3 of the 11 patients in the control group (27%) (incidence rate, 0.66 per patient-year in the rituximab group and 0.60 per patient-year in the control group). Antibiotic prophylaxis was used in 22 of the 33 patients in the rituximab group (67%) and in 8 of the 11 patients in the control group (73%). Pneumocystis pneumonia did not develop in any of the patients.

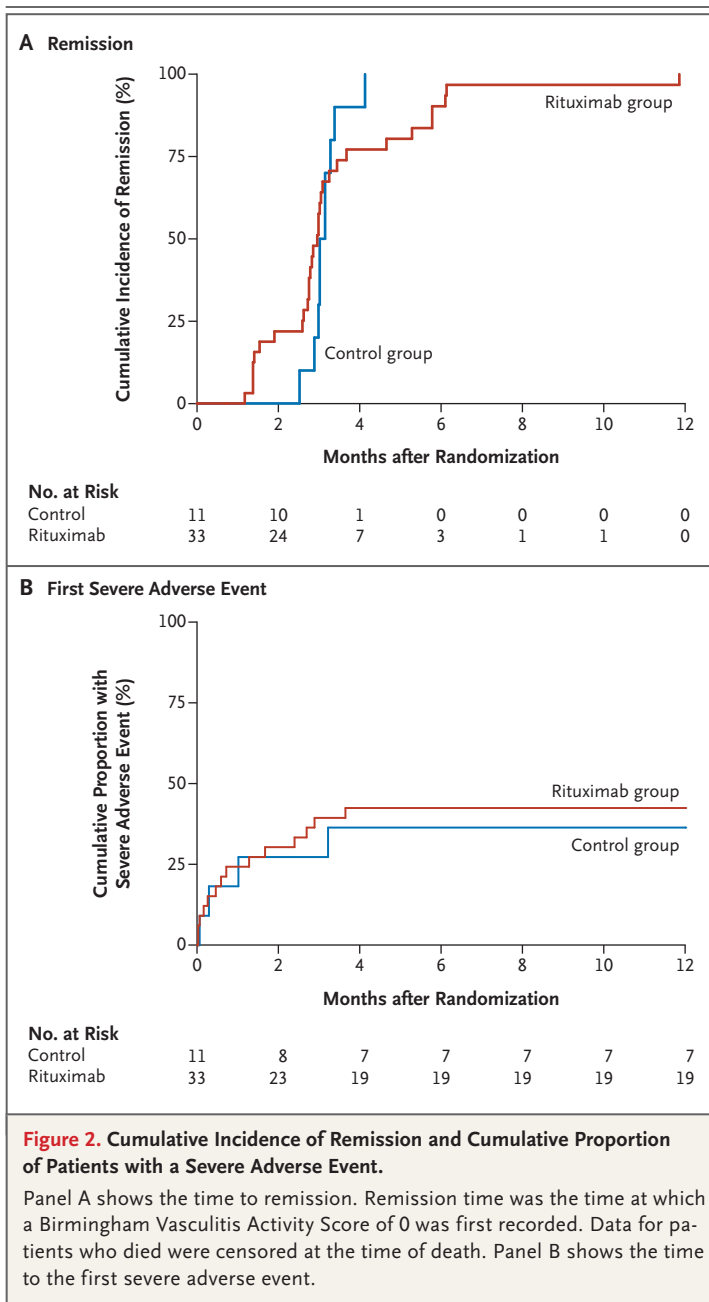
Six of the 33 patients in the rituximab group (18%) and 2 of the 11 patients in the control group (18%) died ($P=1.00$). The median time to death was 81 days (range, 22 to 330 in the rituximab group and 2 to 601 in the control group). The median age at death was 76 years (range, 63 to 84 in the rituximab group and 76 to 82 in the control group), and the GFR at study entry among patients who died was 9 ml per minute (range, 0 to 29 in the rituximab group and 0 to 9 in the control group). The causes of death were infections (in 3 patients in the rituximab group and in 1 patient in the control group), cardiovascular disease (in 1 patient in the rituximab group and in 1 patient in the control group), and complications of end-stage renal failure (in 2 patients in the rituximab group). Serious and severe adverse events and death were common among the 9 patients who were dependent on dialysis at study entry: 3 patients (33%) died, 6 patients (67%) had at least one severe adverse event, and 7 patients (78%) had at least one serious adverse event.

Table 1. Demographic and Clinical Characteristics of the Patients at Trial Entry.*

Variable	Rituximab Group (N=33)	Control Group (N=11)
Age — yr		
Median	68	67
Interquartile range	56–75	58–76
Male sex — no. (%)	17 (52)	6 (55)
Diagnosis — no. (%)		
Wegener's granulomatosis	18 (55)	4 (36)
Microscopic polyangiitis	12 (36)	4 (36)
Renal-limited vasculitis	3 (9)	3 (27)
Proteinase 3 and myeloperoxidase–ANCA binding — U/ml		
Median	53	79
Interquartile range	14–100	28–163
ANCA-positive labeling pattern — no. (%)		
Cytoplasmic	20 (61)	5 (45)
Perinuclear	13 (39)	6 (55)
Glomerular filtration rate — ml/min/1.73 m ² †		
Median	20	12
Interquartile range	5–44	9–33
Organs involved — no.		
Median	3	2
Interquartile range	1–4	1–4
Birmingham Vasculitis Activity Score		
Median	19	18
Interquartile range	14–24	12–25
C-reactive protein — mg/dl		
Median	28	25
Interquartile range	12–87	7–87
Erythrocyte sedimentation rate — mm/hr		
Median	52	64
Interquartile range	14–82	21–106
Dialysis required at entry — no. (%)	8 (24)	1 (9)
Intravenous methylprednisolone — g		
Median	1	1
Interquartile range	1–1	1–1
Use of plasma exchange — no. (%)	8 (24)	3 (27)

* ANCA denotes antineutrophil cytoplasmic antibody.

† The glomerular filtration rate was 0 ml per minute among patients who underwent dialysis.



SECONDARY OUTCOMES

Laboratory Data and Disease Activity

B-cell depletion (defined as $<2 \times 10^6$ cells per liter) occurred in 82% of the patients in the rituximab group by 6 weeks and was sustained in 75% of the patients in this group at 12 months. A total of 64% of the patients in the control group also had B-cell depletion at some point during the study. Doses of prednisolone were reduced in both groups in accordance with the protocol; 96% of patients

in the rituximab group and 89% of patients in the control group were receiving 5 mg per day by 9 months. At 12 months, the median weight-adjusted doses of prednisolone were 0.071 mg per kilogram per day (interquartile range, 0.062 to 0.082) in the rituximab group and 0.082 mg per kilogram per day (interquartile range, 0.071 to 0.093) in the control group ($P=0.78$) (Fig. 3A).

Remission (BVAS of 0 for 2 months) occurred in 30 of the 33 patients in the rituximab group (91%) and 10 of the 11 patients in the control group (91%). The median BVAS decreased from 19 (interquartile range, 14 to 24) at study entry to 0 (interquartile range, 0 to 1.5) at 3 months in the rituximab group and from 18 (interquartile range, 12 to 25) at study entry to 0 (interquartile range, 0 to 0) at 3 months in the control group (Fig. 3B).

In the rituximab group, the median estimated GFR increased from 20 ml per minute per 1.73 m^2 of body-surface area (interquartile range, 5 to 44) at study entry to 39 ml per minute per 1.73 m^2 (interquartile range, 20 to 45) at 12 months. In the control group, the estimated GFR increased from 12 ml per minute per 1.73 m^2 (interquartile range, 9 to 33) at study entry to 27 ml per minute per 1.73 m^2 (interquartile range, 12 to 47) at 12 months. ($P=0.14$ for the comparison of medians.) The mean change in the estimated GFR was 5 ml per minute greater in the rituximab group than in the control group (95% CI, -9 to 19 ; $P=0.49$). Myeloperoxidase and proteinase 3 staining of renal-biopsy specimens for ANCA binding showed reductions in both groups, with negative results in all patients in the rituximab group and in 8 of 10 patients in the control group (80%). At 12 months of follow-up, 4 of 27 patients in the rituximab group (15%) and 1 of 10 patients in the control group (10%) had had a relapse ($P=0.70$).

Quality of Life and Disease Damage

The median change in the score on the Vasculitis Damage Index did not differ significantly between the two treatment groups; the score changed by 2 points (interquartile range, 0 to 3) in the rituximab group and by 1 point (interquartile range, 0 to 2) in the control group ($P=0.38$). The change in the score on the physical component of the SF-36 also did not differ significantly between the two groups ($P=0.36$). The control group had a significantly better outcome than the rituximab

Table 2. Adverse Events.*

Events	Rituximab Group (N=33)		Control Group (N=11)	
	All Events	Patients with ≥1 Event	All Events	Patients with ≥1 Event
	no.	no. (%)	no.	no. (%)
Grade 1–5 events†				
Grade 1 or 2	37	21 (64)	14	6 (55)
Grade 3, 4, or 5	31	14 (42)	12	4 (36)
All	68	25 (76)	26	7 (64)
Serious events				
Events requiring hospitalization or life-threatening events	27	12 (36)	9	4 (36)
Cancer	2	2 (6)‡	0	0
Death	6	6 (18)	2	2 (18)
All	35	16 (48)	11	4 (36)
Types of events				
Serious infections	7	6 (18)	3	2 (18)
All infections	19	12 (36)	7	3 (27)
All infusion reactions	2	2 (6)	0	0
Hematologic events				
Anemia	2	2 (6)	2	2 (18)
Neutropenia	2	2 (6)	1	1 (9)
Thrombocytopenia	1	1 (3)	0	0
Hypogammaglobulinemia	1	1 (3)	0	0

* For deaths and cancer, results are counted as all events until the last follow-up visit. For all other events, results are counted as all events until the follow-up visit at 12 months.

† Adverse events were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

‡ Melanoma developed in one woman (71 years of age) at 9 months, and breast cancer developed in one woman (60 years of age) at 14 months.

group with respect to the change in the score on the mental component of the SF-36 ($P=0.04$), but this difference was accounted for by two influential outliers in the rituximab group. Censoring of data for these two patients eliminated the significant result ($P=0.32$).

DISCUSSION

There is an important unmet need for safer and more effective therapies in patients with ANCA-associated vasculitis, especially those at highest risk for treatment toxicity and death, such as elderly patients and those with severe renal dysfunction. We investigated the efficacy and safety of a rituximab-based regimen versus a conventional cyclophosphamide regimen as remission-induction therapy for ANCA-associated renal vasculitis. The

rituximab-based regimen was not superior to the conventional cyclophosphamide regimen. Both treatment groups had high rates of sustained remission with high rates of severe adverse events.

Sustained-remission rates were not superior in the rituximab group. In both groups, more than 90% of survivors had sustained remission. These rates are similar to those reported in previous studies. Our trial was unblinded. However, renal involvement was the predominant manifestation of disease, and we used objective measurements (e.g., creatinine levels) to assess renal function. Furthermore, there was no evidence of bias with respect to concomitant treatments, and adherence to the corticosteroid-reduction protocol was good. In addition, there was independent adjudication of outcomes.

Only 2 of 27 survivors in the rituximab group

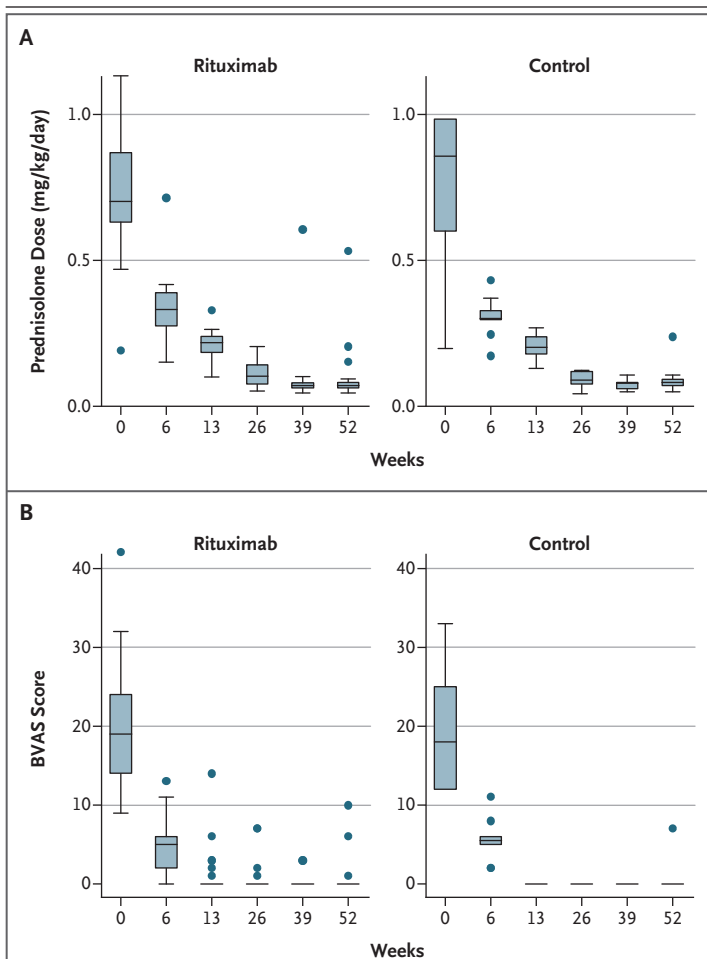


Figure 3. Changes in Prednisolone Dose and Birmingham Vasculitis Activity Score (BVAS), According to Study Group.

Panel A shows changes in the weight-adjusted doses of prednisolone, and Panel B shows changes in the BVAS during the 12-month follow-up of patients in the rituximab and control groups. The circles indicate outliers. The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the 5th and 95th percentiles.

did not have a sustained remission. High-dose glucocorticoids and two doses of cyclophosphamide contributed to the initial responses but were unlikely to have been sufficient to account for the sustained disease control seen in the majority of patients in the rituximab group. Uncontrolled studies have shown an efficacy rate of 80 to 90% with rituximab treatment in refractory ANCA-associated vasculitis; this rate was sustained for 12 months on average.¹⁷⁻²³ In this trial, the sustained responses in patients in the rituximab group were probably attributable to a long-lasting effect of early rituximab treatment. We did

not, however, assess the duration of remission beyond 12 months or the value of repeated administration of rituximab to maintain remission.

Cyclophosphamide is a recommended component of induction therapy for ANCA-associated vasculitis with major organ involvement^{1,33}; however, its use is complicated by infections, cancer, and infertility.^{5,34} To minimize cyclophosphamide toxicity, treatment regimens have been optimized by switching to an alternative drug for remission maintenance or by using pulsed administration; both approaches reduce the cumulative exposure to cyclophosphamide.^{2,3} The use of rituximab offers the opportunity to further reduce exposure to cyclophosphamide.

Rituximab has not been associated with a significant increase in infectious complications when used in combination with methotrexate for the treatment of rheumatoid arthritis⁹ or with chemotherapy for the treatment of non-Hodgkin's lymphoma.³⁵ Furthermore, the use of rituximab, unlike cyclophosphamide, rarely results in profound leukopenia. However, in this trial, the rituximab-based regimen was not associated with lower rates of early severe adverse events than the cyclophosphamide-based regimen, and no difference in safety was observed.

Older age and a lower GFR are strong predictors of death among patients with ANCA-associated vasculitis.³⁶ Rapidly progressive glomerulonephritis is most common in elderly patients. Previous trials have excluded elderly patients. Our inclusion of elderly patients, with no upper age limit, provided a more accurate reflection of the population of patients with severe disease. Mortality was the same in the two treatment groups and was consistent with the 18% rate of death reported in a large cohort study involving patients with ANCA-associated renal vasculitis,³⁶ as well as the rates of death in other trials involving patients with ANCA-associated renal vasculitis.²⁻⁴ In this trial, 50% of deaths were attributed to infection, and the majority of deaths occurred early in treatment (before 3 months). Up to 6 weeks from trial entry, the two groups received the same glucocorticoid and cyclophosphamide regimens; two initial cyclophosphamide pulses were given with the rituximab regimen because of the inclusion of patients with rapidly progressive glomerulonephritis and the lack of experience with rituximab as primary therapy in such patients. Thus, any advantages of rituximab may be seen

not in the initial period of disease management but in longer-term follow-up, with the avoidance of large cumulative doses of cyclophosphamide and maintenance immunosuppression.

Rituximab exerts its effect predominantly through B-cell depletion. Part of cyclophosphamide's therapeutic effect may be mediated through control of B-cell autoreactivity by means of B-cell suppression.³⁷ B-cell-derived ANCA is implicated in the pathogenesis of vasculitis, and ANCA negativity after induction therapy is associated with a reduced risk of relapse.³⁸ This trial provides support for a role of B cells in the pathogenesis of ANCA-associated vasculitis, since the B-cell depletion with rituximab was associated with a clinical response and all patients in the rituximab group became ANCA-negative by 6 months. The rate of ANCA negativity in this trial was higher than that observed with cyclophosphamide regimens in previous studies.² However, the disruption of other B-cell functions, including antigen presentation and T-cell costimulation, may also contribute to the therapeutic mechanism of rituximab.

In conclusion, we found that a rituximab-based regimen was not superior to a conventional cyclophosphamide regimen when used as induction treatment in patients with ANCA-associated renal vasculitis. Remission rates were high with both regimens. However, the rituximab regimen was not associated with a reduction in early severe adverse events, and both regimens were associated with 18% mortality. The use of rituximab permits reduced exposure to cyclophosphamide

and the avoidance of maintenance immunosuppression. Larger trials are needed to confirm our findings, and it is important to determine whether the potential benefits of rituximab translate into improvements in efficacy and safety over the long term.

Supported by Cambridge University Hospitals National Health Service Foundation Trust, a research grant from F. Hoffmann-La Roche, which also provided rituximab for the study, a Kidney Research Scientist Core Education and National Training Program award from the Canadian Institute of Health Research, grants from the Kidney Foundation of Canada and the Canadian Society of Nephrology, and a Clinical Fellowship Award from the Alberta Heritage Foundation for Medical Research (all to Dr. M. Walsh).

Dr. Jones reports receiving lecture fees from F. Hoffmann-La Roche; Dr. Jayne, consulting and lecture fees from F. Hoffmann-La Roche; Dr. Cohen Tervaert, lecture fees and book royalties from F. Hoffmann-La Roche; Dr. Tesar, travel support from F. Hoffmann-La Roche; Dr. Luqmani, consulting fees from Schering-Plough and F. Hoffmann-La Roche and travel support from Wyeth, F. Hoffmann-La Roche, and Abbott; and Dr. Savage, consulting fees from Biogen Idec and GlaxoSmithKline and a paid sabbatical at GlaxoSmithKline after the completion of this study. Addenbrooke's Hospital has received grant support and lecture fees from F. Hoffmann-La Roche for services provided by Dr. Jayne. The University of Birmingham has received grant support from Biovitrum and Talecris for services provided by Dr. Savage. No other potential conflict of interest relevant to this article was reported.

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

We thank the National Institute for Health Research Cambridge Biomedical Research Centre, Dr. Afzal Chaudhry of Addenbrooke's Hospital for developing the trial database, Drs. Annelies Berden and Ingeborg Bajema of Leiden University Medical Center for histologic review of renal-biopsy specimens, all the physicians and nursing staff who contributed to this trial, especially Denise Brown of the Nuffield Orthopaedic Centre, Jo Gray and the Wellcome Trust Clinical Research Facility in Birmingham, Frances Skilton of the Royal Adelaide Hospital, Karen Dahlveen of Addenbrooke's Hospital, and the primary and secondary care physicians who referred patients for this trial.

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