Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis with Renal Involvement

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ABSTRACT

Rituximab (RTX) is non-inferior to cyclophosphamide (CYC) followed by azathioprine (AZA) for remission-induction in severe ANCA-associated vasculitis (AAV), but renal outcomes are unknown. This is a post hoc analysis of patients enrolled in the Rituximab for ANCA-Associated Vasculitis (RAVE) Trial who had renal involvement (biopsy proven pauci-immune GN, red blood cell casts in the urine, and/or a rise in serum creatinine concentration attributed to vasculitis). Remission-induction regimens were RTX at 375 mg/m^2 × 4 or CYC at 2 mg/kg/d. CYC was replaced by AZA (2 mg/kg/d) after 3–6 months. Both groups received glucocorticoids. Complete remission (CR) was defined as Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG)=0 off prednisone. Fifty-two percent (102 of 197) of the patients had renal involvement at entry. Of these patients, 51 were randomized to RTX, and 51 to CYC/AZA. Mean eGFR was lower in the RTX group (41 versus 50 ml/min per 1.73 m^2; P=0.05); 61% and 75% of patients treated with RTX and 63% and 76% of patients treated with CYC/AZA achieved CR by 6 and 18 months, respectively. No differences in remission rates or increases in eGFR at 18 months were evident when analysis was stratified by ANCA type, AAV diagnosis (granulomatosis with polyangiitis versus microscopic polyangiitis), or new diagnosis (versus relapsing disease) at entry. There were no differences between treatment groups in relapses at 6, 12, or 18 months. No differences in adverse events were observed. In conclusion, patients with AAV and renal involvement respond similarly to remission induction with RTX plus glucocorticoids or CYC plus glucocorticoids.

ANCA-associated vasculitis (AAV) (granulomatosis with polyangiitis [GPA; formerly Wegener] and microscopic polyangiitis [MPA]) is a group of progressive, immune-mediated inflammatory diseases that can lead to multiorgan failure and death.[1] Renal involvement occurs in up to 85% of patients with AAV.[2,3] The prognosis of AAV has improved with the use of high-dose glucocorticoids and cyclophosphamide (CYC); however, not all patients respond to CYC, and at least 50% of patients who respond to initial treatment experience relapse within 5 years.[2,4]

The Rituximab for ANCA-Associated Vasculitis (RAVE) Trial was a multicenter, randomized, double-blind, double-dummy, placebo-controlled investigation that compared head-to-head a remission induction regimen on the basis of rituximab (RTX) with one on the basis of CYC followed by azathioprine (AZA). The RAVE Trial showed that RTX plus glucocorticoids was noninferior to conventional immunosuppression for remission induction.[5] Complete remission with successful withdrawal of glucocorticoid therapy at 6 months was achieved in 64% and 53% of the RTX and CYC/AZA groups, respectively.[5] The RTX-based remission induction regimen was more efficacious for inducing remission among patients with relapsing disease,[5] and there was no difference between the two regimens in adverse events at 6 months.[5] On the strength of these results, RTX has been approved for remission induction in severe AAV (defined as presence of one or more major Birmingham Vasculitis Activity Score/Wegener Granulomatosis [BVAS/WG] items or deemed severe enough to require treatment with CYC for remission induction according to standard of care before completion of the RAVE Trial) by regulatory agencies in North America, Europe, and Asia. In addition, follow-up data from the RAVE Trial showed that a single course of RTX was as effective as continuous therapy with CYC and AZA for the maintenance of remission over an 18-month period.[6] Risk factors for relapse include a history of relapsing disease, presence of ANCA directed against proteinase-3 (PR3; as opposed to myeloperoxidase [MPO]), and diagnosis of GPA rather than MPA.[6]

For the past 4 decades, the combination of CYC and high-dose glucocorticoids has been the principal remission induction regimen in AAV. However, some clinicians have been reluctant to alter this approach for patients with ANCA-associated GN in the absence of evidence that a regimen on the basis of RTX is equally effective in AAV patients with renal involvement. A majority of patients in the RAVE Trial had renal involvement at baseline, and approximately one half of the patients in both groups met prespecified criteria for renal involvement.[7,8] A significant proportion of patients in each arm had Cockcroft–Gault estimated creatinine clearance (e-CrCl)<50 ml/min, and the 18-month follow-up data showed similar increases in e-CrCl over time in both arms.[6] The RAVE Trial was not powered to determine efficacy of remission induction in patients with renal involvement, and there were no prespecified renal end points. In this *post hoc* analysis from the RAVE Trial, we analyzed patients with renal involvement to provide evidence about remission induction in

AAV from a head-to-head, randomized, blinded comparison of an RTX-based regimen with a regimen based on CYC/AZA.

RESULTS

Patients
In total, 102 (52%) of 197 patients enrolled had renal involvement. We defined renal involvement as at least one of the following findings: (*1*) active, biopsy-proven, pauci-immune GN (*n*=45); (*2*) red blood cell casts on urine microscopy; (*3*) rise in serum creatinine>30% (or >25% decline in creatinine clearance) that was attributed to active AAV in the kidney; and (*4*) serum creatinine<4.0 mg/dl. Among patients with renal involvement, 51 patients were assigned to RTX/placebo, and 51 patients were assigned to CYC/AZA.

The baseline characteristics of 102 patients with renal involvement are listed in Table 1. The extrarenal manifestations of these patients are shown in Table 2. The treatment groups were balanced with respect to AAV diagnosis, ANCA type, baseline BVAS/WG, disease duration, and exposure to CYC before trial entry; 58 (57%) patients had new diagnoses of AAV, 44 (43%) patients had relapsing disease, 68 (67%) patients had GPA, and 34 (33%) patients had MPA. A higher percentage of patients in the RTX group had relapsing disease at baseline, but this difference was not statistically significant (49% versus 37%, *P*=0.23). The baseline eGFR was significantly lower in the RTX group compared with the CYC/AZA group, and this difference was statistically significant (41 versus 50 ml/min per 1.73 m^2, *P*=0.05). Similar results were obtained when creatinine clearance was calculated by the Cockcroft–Gault equation (54 versus 71 ml/min, *P*=0.01); 82% of patients in the RTX group and 67% of those in the CYC/AZA group had eGFR values<60 ml/min per 1.73 m^2 at trial entry (*P*=0.07).

At 18 months, 63% of patients with renal involvement in the RTX group and 67% of those in the CYC/AZA group remained in the treatment arm to which they had been assigned (*i.e.*, did not meet criteria for early treatment failure, did not crossover to the other treatment arm, did not suffer a severe disease relapse that required open-label retreatment with RTX per protocol, and did not switch to best medical judgment therapy or withdraw from the trial for other reasons). No patient was lost to follow-up.

End Points
Complete Remission at 6, 12, and 18 Months
At 6 months, 39 (77%) patients with renal involvement in the RTX arm and 42 (82%) patients with renal involvement in the CYC/AZA arm completed treatment as randomized (*P*=0.46); 31 (61%) patients treated with RTX and 32 (63%) patients treated with CYC/AZA achieved the primary outcome of complete remission defined as a BVAS/WG=0 and successful completion of the prednisone taper at 6 months (*P*=0.84); 38 (75%) patients in the RTX group and 39 (77%) patients in the CYC/AZA group achieved complete remission at some

Table 1. Baseline demographic and clinical characteristics of the patients with renal involvement

Variable	RTX Group (n=51)	CYC/AZA Group (n=51)	P Value
Age (yr) mean (SD)	56 (15)	54 (13)	0.32
Sex (%)			0.32
Men	47	57	
Women	53	43	
Race (%)			
White	94	94	
Black	4	4	
Other	2	2	
Body mass index (kg/m^2) mean (SD)	28 (5)	29 (6)	0.56
Type of AAV (%)			0.67
GPA	69	65	
MPA	31	35	
ANCA type (%)			0.69
PR3	59	55	
MPO	41	45	
Newly diagnosed GN at enrollment (%)	51	63	0.23
Pre-enrollment disease duration in those with relapsed GN (yr) mean (SD)	5.7 (4.5)	4.3 (4.1)	0.28
Pre-enrollment exposure to CYC in patients with relapsed GN (%)	84	68	0.29
BVAS/WG (0–67) mean (SD)	8.7 (2.74)	8.7 (3.51)	0.54
Renal BVAS/WG (0–7) mean (SD)	4.6 (1.44)	4.5 (1.42)	0.68
Serum creatinine at entry (mg/dl) mean (SD)	2.02 (0.92)	1.71 (0.70)	0.11
MDRD eGFR at entry (ml/min per 1.73 m^2) mean (SEM)	41.4 (3.3)	50.4 (3.3)	0.05
MDRD GFR>60 ml/min per 1.73 m^2 (%)	18	34	0.19
MDRD GFR=30–60 ml/min per 1.73 m^2 (%)	47	39	
MDRD GFR<30 ml/min per 1.73 m^2 (%)	35	27	
Vasculitis Damage Index (0–64) mean (SD)	1.1 (1.39)	0.8 (1.17)	0.34
C-reactive protein (mg/dl) median and quartiles 1–3	1.4 (0.5–4.6)	2.0 (0.7–5.1)	0.23
Erythrocyte sedimentation rate (mm/h) mean (SD)	43.2 (25.85)	53.7 (29.27)	0.07
Serum albumin (g/dl) mean (SD)	3.54 (0.45)	3.57 (0.45)	0.51
Number of organs involved mean (SD)	3.2 (1.17)	3.2 (1.39)	0.63
Alveolar hemorrhage (%)	35	29	0.53

Table 2. Baseline extrarenal organ involvement

| Organs (%)	RTX Group (n=51)	CYC/AZA Group (n=51)	P Value
HEENT	49	45	0.84
Joints	43	49	0.69
Lungs	51	49	>0.99
Nervous system	18	8	0.23
Skin	28	20	0.48
Mucus membrane/eyes	12	18	0.58
Gastrointestinal tract	2	0	>0.99
Heart	2	0	>0.99

HEENT, head, eyes, ears, nose and throat.

point during 18 months of treatment according to protocol (P=0.82). The mean time (SD) to complete remission was 182 (43) days in the RTX group and 202 (66) days in the CYC/AZA group (P=0.07). The median time (interquartile range) to renal remission was 56 (26–182) days in the RTX group and 35 (27–177) days in the CYC/AZA group (P=0.21); 41 (80%) patients treated with RTX achieved remission while receiving <10 mg/d prednisone compared with 43 (84%) patients in the

CYC/AZA group (P=0.60). There was no difference in the duration of remission between the two groups (P=0.32) (Figure 1).

At 12 months, 23 (45%) patients in the RTX arm and 24 (47%) patients in the CYC/AZA arm remained in complete remission (P=0.84). The same comparison at 18 months revealed that 21 (41%) patients in the RTX group and 22 (43%) patients in the CYC/AZA group were still in complete remission (P=0.84). No differences in the complete remission rates at 6, 12, and 18 months were observed when the analyses were stratified by ANCA type, AAV diagnosis, or new diagnosis (Table 3).

Treatment Failures Caused by Uncontrolled Disease
Among patients with renal involvement, seven of 102 (6.9%) patients were declared treatment failures because of uncontrolled disease at 1 month. All seven patients with uncontrolled disease (five patients on RTX and two patients on CYC/AZA) were PR3 ANCA–positive and had clinical diagnoses of GPA. Uncontrolled disease was caused by progressive renal disease in five patients, alveolar hemorrhage in one patient, and multiorgan failure in one patient. These patients were considered failures for the primary outcome at 6 months and all other time points.
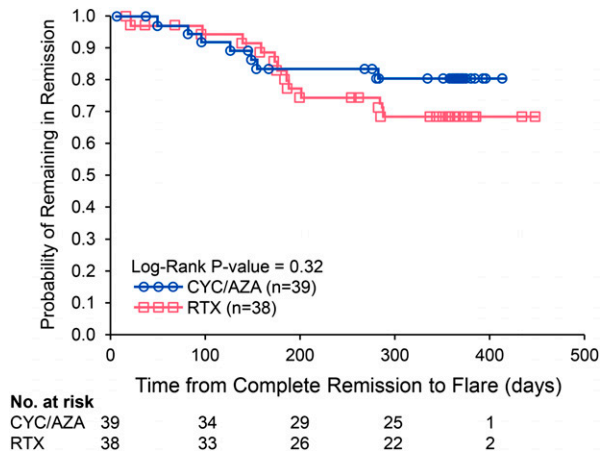
Figure 1. Kaplan–Meier plots for the risk of disease relapse after achieving complete remission. The time to first disease relapse after achieving complete remission by treatment (RTX versus CYC/AZA) is shown. Subjects are censored at termination, 18 months post-randomization, or the time of treatment change by blinded cross-over, best medical judgment, or open-label RTX treatment. Only subjects achieving complete remission are included in this analysis, which is defined as achieving a BVAS/WG score=0 while not on prednisone. The P value is from a log-rank test and compares the survival curves of the treatment arms.

Table 3. Complete remission rates at 6, 12, and 18 months stratified by disease type, ANCA type, and new versus relapsing disease

Complete Remission Rates (%)	RTX Group (n=51)	CYC/AZA Group (n=51)	P Value
GPA, mo (n=68)	35	33	
6	66	64	0.86
12	43	52	0.48
18	40	46	0.65
MPA, mo (n=34)	16	18	
6	50	61	0.52
12	50	39	0.52
18	44	39	0.77
PR3 ANCA, mo (n=58)	30	28	
6	67	61	0.64
12	40	46	0.62
18	37	46	0.45
MPO ANCA, mo (n=44)	21	23	
6	52	65	0.39
12	52	48	0.76
18	48	39	0.57
New diagnosis, mo (n=58)	26	32	
6	50	69	0.15
12	42	59	0.20
18	42	53	0.41
Relapsing disease, mo (n=44)	25	19	
6	72	53	0.19
12	48	26	0.14
18	40	26	0.34

Blinding was maintained in all but one subject with uncontrolled disease, and the patients were treated according to best medical judgement, which, at the time that the trial began, generally consisted of CYC and glucocorticoids. Thus, four patients meeting criteria for early treatment failure received CYC and glucocorticoids as salvage therapy, with three of four patients achieving remission. Two patients received CYC, glucocorticoids, and plasma exchange, with one patient achieving remission. One patient suffered multiorgan failure and died because of sepsis, and one patient received RTX, glucocorticoids, and plasma exchange, and achieved disease remission.

Renal Function
Improvement in Renal Function
The mean (SEM) eGFR among patients in the RTX group with renal involvement increased from 41 ml/min per 1.73 m^2 ($\pm$3.3) at baseline to 49 ml/min per 1.73 m^2 ($\pm$3.4) at 18 months (P=0.05 comparing baseline eGFR with 18-month values). In the CYC/AZA group, the mean (SEM) eGFR increased from 50 ml/min per 1.73 m^2 ($\pm$3.3) at baseline to 57 ml/min per 1.73 m^2 ($\pm$3.4) at 18 months (P=0.05) (Figure 2). Similar results were obtained using e-CrCl values (Supplemental Table 1). When stratified by eGFR at baseline, there were no significant differences in the mean eGFR increase between the two treatment groups (Table 4). Figure 3 shows the change for each individual patient in eGFR between baseline and 18 months.

Patients with MPA or MPO ANCA had a lower baseline eGFR compared with those with GPA or PR3 ANCA (36 versus 51 ml/min per 1.73 m^2 [MPA versus GPA], P<0.01 and 40 versus 51 ml/min per 1.73 m^2 [MPO ANCA versus PR3 ANCA], P=0.02, respectively). However, there was no difference between ANCA types, AAV diagnoses, or newly diagnosed versus relapsing disease concerning eGFR change over time (P=0.66, P=0.05, and P=0.90, respectively).

### Progression to Renal Disease
Three patients who did not have renal involvement at baseline progressed to renal involvement over the course of the trial. Two patients in the RTX group developed renal relapses at months 7 and 16, and one patient in the CYC/AZA group experienced a renal relapse at month 18.

ESRD
Two patients randomized to CYC/AZA required RRT at 18 months. Their baseline eGFR values were 22 and 18 ml/min per 1.73 m^2. These patients had gradual progression of their chronic renal injury and not relapses of GN during the trial.

Outcomes in Patients with Biopsy-Proven GN
Forty-five (44%) patients with renal involvement in this cohort had biopsy-confirmed GN. Their mean BVAS/WG (disease activity) scores were lower than those of patients with renal involvement diagnosed clinically who did not undergo renal biopsy (7.8 versus 9.4, P<0.01). The patients who did not
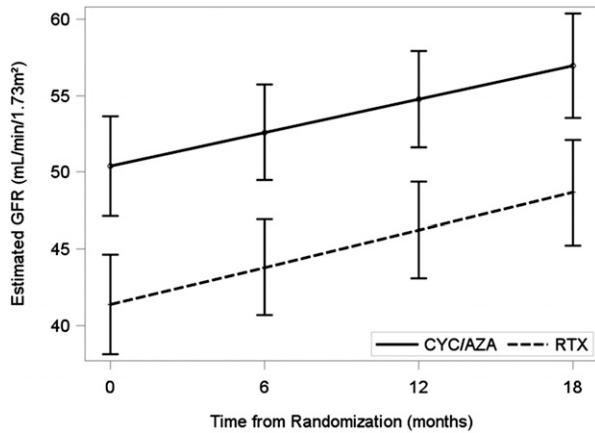
Figure 2. eGFR at baseline and 6, 12, and 18 months post-randomization. Estimates for the mean and SEM in eGFR (milliliters per minute per 1.73 m^2) at baseline and 6, 12, and 18 months postrandomization for each treatment arm (RTX versus CYC/AZA) are shown. GFR is estimated using the MDRD method. The results are obtained from a random regression model with fixed effects for treatment assignment, time, type of diagnosis, ANCA status at baseline, an indicator of new diagnosis versus relapsing disease at baseline, and random effects for treatment group intercepts and linear trends over time. All data through month 18, termination, or treatment change by blinded crossover, best medical judgment, or open-label RTX treatment, whichever is earliest, are included in the model.

Table 4. eGFR (milliliters per minute per 1.73 m^2) by MDRD at baseline and 6, 12, and 18 months stratified by baseline eGFR

Mean (SEM) eGFR, ml/min per 1.73 m^2	RTX Group (n=51)	CYC/AZA Group (n=51)	P Value
Baseline eGFR>60	9	10	
Baseline	80.1 (8.40)	76.6 (6.01)	0.74
6 mo	78.7 (7.50)	76.4 (5.33)	0.81
12 mo	77.3 (6.84)	76.2 (4.80)	0.90
18 mo	75.9 (6.52)	76.0 (4.46)	0.99
Comparison between 18 mo and baseline, P value	<0.01	0.20	
Treatment difference over time, P value			0.54
Baseline eGFR=30–60	24	20	
Baseline	39.5 (2.10)	46.6 (2.31)	0.03
6 mo	42.9 (2.49)	50.5 (2.72)	0.05
12 mo	46.4 (3.24)	54.4 (3.51)	0.10
18 mo	49.9 (4.16)	58.3 (4.50)	0.18
Comparison between 18 mo and baseline, P value	<0.01	<0.01	
Treatment difference over time, P value			0.80
Baseline eGFR<30	18	14	
Baseline	24.4 (1.66)	25.5 (1.88)	0.66
6 mo	26.3 (2.22)	28.0 (2.50)	0.61
12 mo	28.1 (3.32)	30.5 (3.73)	0.64
18 mo	30.0 (4.58)	33.0 (5.14)	0.67
Comparison between 18 mo and baseline, P value	<0.01	0.09	
Treatment difference over time, P value			0.77

undergo renal biopsy had a numerically higher likelihood of having alveolar hemorrhage (33.3% versus 20%, P=0.18) or mononeuritis multiplex (7% versus 2.2%, P=0.38), accounting for their higher BVAS/WGs and fewer renal biopsies. However, there are differences between these groups in the presence of renal BVAS/WG items at baseline. Patients who had biopsy-proven GN were more likely to have a rise in serum creatinine (78% versus 58%, P=0.04) and/or hematuria (51% versus 32%, P=0.07) compared with those with clinically diagnosed GN, who were significantly more likely to have red blood cell casts (81% versus 56%, P<0.01; data not shown). Comparing renal outcomes of patients with biopsy-proven GN and clinically diagnosed renal involvement, there were no differences in complete remission rates. The increase in eGFR from baseline to 18 months was similar between these two groups (Table 5).

Rate and Number of Disease Relapses

Fourteen (37%) patients with renal involvement in the RTX group experienced a total of 21 limited relapses over 18 months. By comparison, 10 (26%) patients in the CYC/AZA group experienced a total of 11 limited disease relapses over this same period (P=0.35). Seven patients in the RTX group experienced a total of eight severe disease relapses compared with five patients with six severe disease relapses in the CYC group (P=0.54). Of these severe relapses, seven renal relapses occurred in six patients in the RTX group, and three renal relapses occurred in two patients assigned to the CYC/AZA group (P=0.27). The rates of severe relapses in the RTX and CYC/AZA groups per patient-month were 0.011 and 0.008, respectively (P=0.58). The rates of renal relapses per patient-month were 0.010 in the RTX group and 0.004 in the CYC/AZA group (P=0.22).

The mean (SD) time from complete remission to any disease relapse for subjects who reached complete remission was 170 (76) days in the RTX group and 130 (76) days in the CYC/AZA group (P=0.11); 10 (26%) of 38 patients in the RTX group who achieved complete remission experienced 12 disease relapses over the 18-month analysis period—all after completion of the prednisone taper—compared with seven (18%) of 39 patients in the CYC/AZA arm (P=0.38). When stratified by ANCA type or new versus relapsing disease, there were no differences in the rate or number of renal relapses between the two groups. Four patients with MPA treated with RTX, three of whom were MPO ANCA–positive and one of whom was PR3 ANCA–positive, experienced a total of five renal relapses by month 18. In contrast, no renal relapses occurred among patients with MPA in the
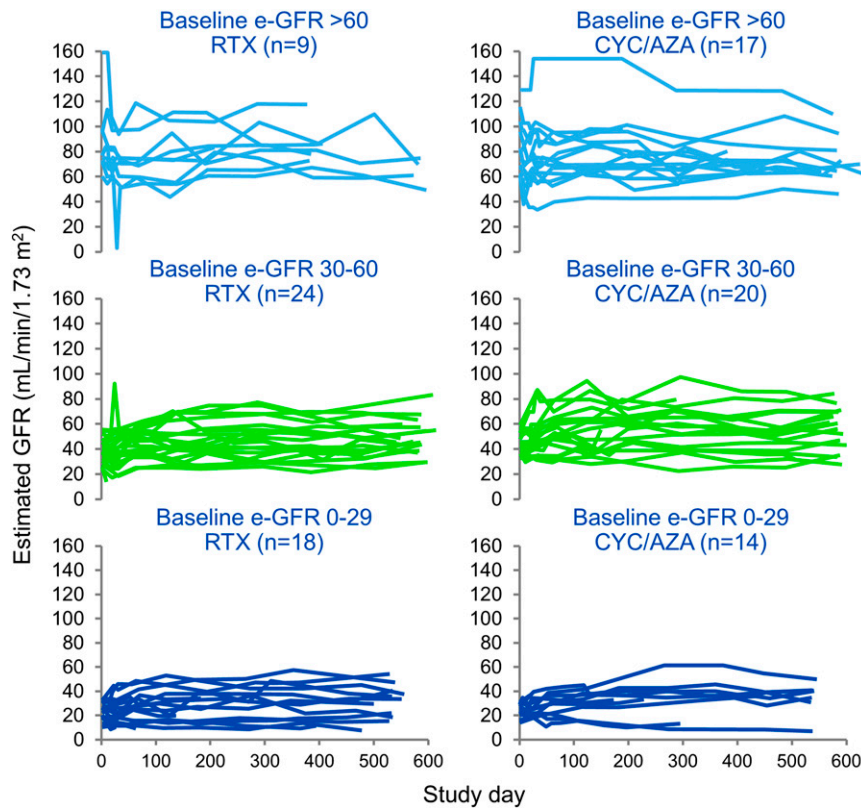
Figure 3. eGFR over time by treatment group and baseline eGFR. eGFR over time per subject stratified by the baseline eGFR for each treatment arm (RTX versus CYC/AZA) is shown. eGFR for subjects having a baseline eGFR (top panels)>60, (middle panels) between 30 and 60, and (bottom panels) <30 ml/min per 1.73 m². All data through month 18, termination, or treatment change by blinded crossover, best medical judgment, or open-label RTX treatment, whichever is earliest, are included. Where no baseline value exists, the screening value is included and set to study day 0.

Table 5. Comparison of outcomes among patients with biopsy-proven and clinically diagnosed renal vasculitis

Outcome	Biopsy-Proven Renal Vasculitis (n=45)		Clinically Diagnosed Renal Vasculitis (n=57)	
	RTX (n=21)	CYC (n=24)	RTX (n=30)	CYC (n=27)
Complete remission at 6 mo (%)	61.9	66.7	60	59.3
Complete remission at 12 mo (%)	57.1	54.2	36.7	40.7
Complete remission at 18 mo (%)	52.4	50	33.3	37.0
eGFR increase from baseline to 18 mo (ml/min per 1.73 m²)	5.70	9.47	8.03	3.65

CYC/AZA group (P=0.04). By comparison, two patients with GPA treated with RTX experienced two renal relapses, and two patients with GPA treated with CYC/AZA experienced a total of three renal relapses (P>0.99) by month 18. There were no differences between the two treatment groups in the overall relapse rates or the numbers of patients who experienced limited or severe disease relapses at 6, 12, or 18 months.

Measurement of Disease-Related Damage and Quality of Life

The Vasculitis Damage Index scores increased by 1.6 points from baseline to 18 months in the RTX group and 1.5 points in the CYC/AZA group. The mean (SD) increase in the score of the physical component of the short form health survey (SF-36) from baseline to 18 months did not differ significantly between the two treatment groups (7.0 [10.94] versus 8.1 [10.92]).

Adverse Events

There were no significant differences between the treatment groups in the numbers of total adverse events, serious adverse events, or infections. Four deaths (two in each group) occurred during the trial; 30 serious adverse events occurred in 21 patients with renal involvement treated with RTX, and 39 such events occurred in 24 patients treated with CYC/AZA (P=0.55). The incidence rates for serious adverse events were 0.04 per patient per month in the RTX group and 0.05 per patient per month in the CYC/AZA group (P=0.36). Twelve episodes of grade 2 or higher leucopenia occurred in the CYC/AZA group compared with five such episodes in the RTX group (P=0.11).

DISCUSSION

This analysis of AAV and renal involvement ranging from mild to severe shows that patients treated with regimens on the basis of either RTX plus glucocorticoids or CYC/AZA plus glucocorticoids have outcomes that are equivalent in nearly every respect over a follow-up period of 18 months. These results were observed, despite the fact that patients randomized to RTX were not retreated prophylactically with RTX after the return of B cells and were not treated with additional immunosuppression agents after the discontinuation of prednisone at 5.5 months. In contrast, patients in the CYC/AZA group received continuous immunosuppression for 18 months.

The definition of renal involvement used in the trial was developed in 1999 as part of the BVAS/WG validation process.[7] This definition includes biopsy-proven GN, urinary red blood cell casts, or substantial declines in renal function. Patients with AAV who meet this definition generally have or are at risk for

rapidly progressive GN. In the absence of timely and effective therapy, they have a high likelihood of progression to ESRD and death.[1] The fact that 82% of patients in the RTX arm with renal involvement (compared with 67% of those in the CYC/AZA arm) had eGFR values <60 ml/min per 1.73 m^2 at trial entry reflects the severity of their baseline renal disease. All patients enrolled in the trial who did not have renal involvement had severe disease in other organ systems (*e.g.*, alveolar hemorrhage, necrotizing scleritis, or vasculitic neuropathy).

The percentage of patients in the RTX group that remained in the group to which they were originally assigned at 18 months without requiring additional glucocorticoids or other therapies was equivalent to that of patients in the CYC/AZA group. In addition, there were no statistically significant differences at any time point between the two groups in the number of patients achieving sustained remission or the numbers of disease relapses. The baseline eGFR was significantly lower in the RTX group compared with the CYC/AZA group. This result was a reflection of the higher percentage of patients in the RTX group who had relapsing disease (49% versus 37%). Other analyses have revealed that three factors are strong predictors of disease relapse: (*1*) a history of previous relapse; (*2*) PR3 ANCA positivity; and (*3*) clinical diagnosis of GPA.[6,9] The patients randomized to RTX were more likely to have one or more of these characteristics at baseline than were their counterparts randomized to CYC/AZA. Nevertheless, the improvement in renal function observed over the course of 18 months in the RTX group was parallel to that observed in the CYC/AZA group.

The importance of glucocorticoids as initial lifesaving and temporizing components of remission induction regimens in AAV with renal involvement should not be underestimated. Being the only fast-acting immunosuppressive agent available, they are effective in stabilizing and improving renal function in many patients. Whereas current guidelines from the Japanese Society of Nephrology suggest that glucocorticoids alone may be sufficient to induce remission in the majority of patients with MPA and renal disease,[10] this is clearly not the case for patients with MPA described in other cohorts[4] and patients with GPA and renal disease. In GPA with renal disease, glucocorticoids could only delay the inevitable fatal outcome,[11] which was changed by the introduction of CYC. Because glucocorticoids were equal in both treatment arms and discontinued by 6 months in most patients, differences in overall and renal outcomes between the treatment arms would have to be attributed to the effects of RTX versus CYC/AZA.

Patients in the RTX arm who remained in remission did not receive any additional therapy for >1 year before the 18-month time point. In contrast, patients in the CYC/AZA arm remained on AZA throughout this time period after their switchover from CYC, which typically occurred between 4 and 6 months. The majority of disease relapses observed in the RTX group occurred after the reconstitution of B cells.[6] Several studies have now shown that retreatment with RTX either at a fixed interval or on the return of detectable B cells and rising ANCA titers is associated with prolongation of the

remission state.[12,13] It is likely that the retreatment of patients whose remissions were induced with RTX at some prescribed interval would increase the percentage of patients who remain in complete remission at 18 months.

Our study did not show significant differences in overall adverse events between the two groups. Several factors account for the absence of differences in adverse events between the groups. First, by definition, the adverse events counted in a clinical trial include both disease- and treatment-related events. Glucocorticoids accounted for many of the adverse effects in both groups, limiting the ability to distinguish differences between the two treatment groups. Second, the short courses of CYC used in this trial coupled with the closely monitored setting of a clinical trial contributed to the fewer adverse events in the CYC/AZA group. Patients in the trial had complete blood counts performed every 2 weeks while on CYC or CYC placebo.

Our study had certain limitations. First, patients with serum creatinine concentrations >4.0 mg/dl could not be enrolled, because insufficient equipoise existed at the time that the trial began to justify the randomization of patients with advanced renal dysfunction to an investigational treatment compared with CYC. Thus, the efficacy of RTX in patients with advanced kidney failure cannot be known from the RAVE Trial results. In this context, it should be noted that the efficacy of RTX for remission induction in patients with advanced kidney failure was shown in the rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) Trial, which differed from the RAVE Trial in being an unblinded trial where RTX was used along with two pulses of intravenous CYC that allowed the use of glucocorticoids for 12 months.[14] In addition, 24% of patients in the RITUXVAS Trial received plasma exchange. Additional data on the use of RTX for remission induction in severe renal disease will be available from the ongoing trial of plasma exchange in AAV, plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis: an international randomized controlled trial (PEXIVAS), which allows the use of RTX for remission induction.[15] We note that CYC itself became regarded as the standard of care not through randomized trials but rather, through observational experience in longitudinal studies.[2,3] Second, patients who were ANCA-negative and those with circulating antiglomerular basement membrane (anti-GBM) antibodies in addition to ANCA were excluded. Consequently, the comparative efficacy of the two regimens remains uncertain for ANCA-negative patients and those who are double positive for ANCA and anti-GBM antibodies. Third, the trial was not powered to detect differences in some subgroups of interest, such as patients with an eGFR<15 ml/min per 1.73 m^2 at baseline. Additional studies are required to understand the full use of RTX in this setting. Fourth, although in AAV, isolated proteinuria is not considered indicative of active disease; in many other forms of glomerular diseases, persistent proteinuria may reflect irreversible glomerular injury. Unfortunately, proteinuria was not quantified in the study.

In conclusion, in this randomized, double-blind, placebo-controlled trial, no significant differences in the renal outcomes over 18 months were observed between an induction regimen based on a single course of RTX plus glucocorticoids compared with continuous treatment for 18 months of a regimen comprised of CYC plus glucocorticoids followed by AZA. These results show that RTX is an appropriate and effective therapy for the induction of remission in many patients with AAV with renal involvement, with the caveat that patients with the most advanced degrees of renal dysfunction were not studied in this trial. Follow-up of our trial cohort beyond the primary end point assessment at 6 months indicates that patients with RTX-induced remissions may benefit from retreatment at some interval. Retreatment with RTX at an appropriate juncture during the remission period has the potential to improve patients' outcomes.

CONCISE METHODS

Patients
Details of the RAVE Trial design have been published.[5,8] The members of the RAVE/Immune Tolerance Network Research Group are listed in the Supplemental Material. Patients were eligible for inclusion in the RAVE Trial if they met the following criteria: (*1*) diagnosis of GPA or MPA, (*2*) positive serum assays for ANCA directed against PR3 or MPO, (*3*) manifestations of severe disease (defined as that which would be treated with CYC and glucocorticoids outside the context of the clinical trial), and (*4*) BVAS/WG≥3.[7] Patients with either newly diagnosed or relapsing disease were eligible for enrollment. Patients with serum creatinine>4 mg/dl, pulmonary hemorrhage requiring mechanical ventilation, and positive anti-GBM antibody were excluded.

Treatment
The treatment protocol has been reported in detail.[5] Randomization was stratified according to ANCA type and clinical site. The two treatment groups received the same glucocorticoid regimen: one to three pulses of 1000 mg methylprednisolone followed by prednisone at a dose of 1 mg/kg per day (not to exceed 80 mg/d). Those in the experimental arm received intravenous RTX (Genentech) at a dose of 375 mg/m² one time per week for 4 weeks combined with high-dose glucocorticoids tapered to 0 mg/d over 6 months and no subsequent maintenance therapy. Those in the control arm received CYC for 3–6 months followed by AZA after remission had been achieved. AZA was continued in the control arm until month 18.

Patients who had severe relapses during the first 6 months were eligible for blinded crossover to the other treatment group. Patients who underwent crossover received the other treatment in full, including the three methylprednisolone pulses. Limited relapses were treated by reinstituting prednisone at a starting dose chosen by the investigator and maintained for 4 weeks followed by the standardized prednisone dose taper.[5,8] Patients were classified as having early treatment failure if, at 1 month, their BVAS/WG had not decreased by at least 1 point or a new manifestation of disease had emerged. Patients with early treatment failure discontinued their assigned treatments and received therapies according to the best medical judgment.

Assessments
Study visits occurred at baseline and weeks 1–4 during the RTX/RTX-placebo infusion followed by visits at months 2, 4, 6, 9, 12, 15, and 18. After 18 months, visits occurred every 6 months until the common closeout date. Serial serum samples were tested for PR3 ANCA and MPO ANCA by direct ELISA.[16] The principal measure of disease activity was the BVAS/WG.[7] Other outcomes assessment instruments included the Vasculitis Damage Index[17] and the SF-36.[18] The four-variable Modification of Diet in Renal Disease (MDRD) was used to estimate GFR.[19] The Cockcroft–Gault method was used to calculate e-CrCl.[20] Proteinuria was not quantitated, and dipstick proteinuria estimates were used instead for the determination of Vasculitis Damage Index scores.

Study Definitions
Renal involvement was defined as active GN with biopsy-proven pauci-immune GN and/or presence of at least one major item on the BVAS/WG score and a serum creatinine<4 mg/dl. Major renal items included red blood cell casts on urinalysis and >30% rise in serum creatinine or >25% decline in creatinine clearance.

Renal function was defined as eGFR calculated by the four-variable MDRD equation.[19] Patients were defined as having uncontrolled disease or early treatment failure if they had a new or worsening BVAS/WG item or a worsening or unchanged overall BVAS/WG 1 month after entry. Complete remission was defined as a BVAS/WG=0 and successful completion of prednisone taper by 6 months. Renal remission was defined as stabilization or improvement in serum creatinine and resolution of hematuria defined as the presence of <10 urinary red blood cells per high power field. A disease relapse was defined as a BVAS/WG≥1 point after achieving a BVAS/WG=0. Disease relapse was defined as severe when one major item on BVAS/WG was scored. Renal relapse was defined by the presence of at least one major item on the renal category of the BVAS/WG. All renal relapses were, by definition, severe relapses. The term limited relapse refers to a nonsevere disease relapse that could be treated with an increase or resumption of the glucocorticoid dose alone rather than treatment with either RTX or CYC.

Outcomes and Follow-Up
Our primary outcome for this *post hoc* analysis was achievement of complete remission. Secondary outcomes were sustained remission at 12 and 18 months, slope of eGFR increase at 18 months, rates of disease relapse, and rates of severe adverse events. All patients were followed until the common closeout date with a minimum follow-up of 18 months.

Statistical Analyses
The analysis sample consisted of all randomized subjects who had renal involvement at baseline. Comparisons of categorical variables were performed using a chi-squared test or a Fisher exact test depending on the cell sizes. Comparisons of continuous variables were performed using a Wilcoxon rank sum test. Rates of disease relapses and adverse events (in person-months) were compared between treatment groups using a Poisson regression model. Comparisons of time-to-event variables between groups were performed using a

log-rank test and described using Kaplan–Meier curves. Descriptive statistics for analyses of selected time-to-event variables were estimated using only those subjects experiencing an event, and comparisons between groups were performed by the Wilcoxon rank sum test. eGFRs were calculated using the four-variable MDRD formula. Comparisons between treatment arms in eGFR values and change over time were performed using a random coefficients mixed model with random effects of intercept and time since randomization. The model was adjusted for dichotomous baseline variables, such as new versus relapsing disease, ANCA type (MPO versus PR3), and AAV diagnosis (MPA versus GPA). All eGFR values up to and including the date of censoring were used in the model. Comparisons between values of dichotomous baseline variables in eGFR at baseline and over time were performed using a random coefficients mixed model, with random effects for intercept and time. All statistical tests were two sided, and a P value <0.05 was considered to indicate statistical significance. The SAS version 9.1 (SAS, Inc., Cary, NC) was used for all statistical analyses.

DISCLOSURES

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See related editorial, "Understanding the Role of Rituximab in ANCA GN: Regressing toward the Mean," on pages 771–774.

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