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Rituximab for the Treatment of Relapses in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. **Disease relapses are frequent in antineutrophil cytoplasmic antibody–associated vasculitis (AAV). This study was undertaken to evaluate outcomes in patients with AAV who are re-treated with rituximab (RTX) and prednisone for severe disease relapses.**

Methods. **The Rituximab in AAV trial was a randomized, double-blind, placebo-controlled trial comparing the rates of remission induction among patients treated with RTX (n = 99) and patients treated with cyclophosphamide (CYC) followed by azathioprine (AZA) (n = 98). Prednisone was tapered to discontinuation after 5.5 months. After remission was achieved, patients who experienced a severe disease relapse between months 6 and 18 were eligible to receive RTX and prednisone on an open-label basis according to a prespecified protocol. Investigators remained blinded with regard to the original treatment assignment.**

Results. **Twenty-six patients received RTX for**

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disease relapse after remission had initially been achieved with their originally assigned treatment. Fifteen of these patients were initially randomized to receive RTX and 11 to receive CYC/AZA. Thirteen (87%) of the patients originally assigned to receive RTX and 10 (91%) originally assigned to receive CYC/AZA achieved remission again with open-label RTX (an overall percentage of 88%). In half of the patients treated with open-label RTX, prednisone could be discontinued entirely. Patients in this cohort experienced fewer adverse events compared to the overall study population (4.7 adverse events per patient-year versus 11.8 adverse events per patient-year).

***Conclusion*. Re-treatment of AAV relapses with RTX and glucocorticoids appears to be a safe and effective strategy, regardless of previous treatment.**

Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAVs) that affect small and medium-sized blood vessels. Treatment of systemic AAV with cyclophosphamide (CYC)–based regimens combined with high-dose glucocorticoids has been found to dramatically alter the prognosis in this group of diseases but is associated with significant concerns about treatment-related morbidity, particularly infection, infertility, and long-term risk of malignancy (1–3). The Rituximab in AAV (RAVE) trial demonstrated that a regimen of rituximab (RTX) plus glucocorticoids is noninferior to CYC plus glucocorticoids followed by azathioprine (AZA) for remission induction in severe AAV (4). This trial also demonstrated superiority of the RTX regimen for remission induction in patients with relapsing disease.

In a large majority of patients with AAV, disease remission is now achieved with regimens based on either RTX or CYC, but relapses remain common. Previous studies have demonstrated the occurrence of relapses in up to 55% of patients within the first 3 years after remission and a persistent risk of relapse over long-term followup (5,6). In addition, remission induction regimens fail in a substantial percentage of patients, with persistent or recurrent active AAV within the first 6 months of remission induction therapy, regardless of whether RTX- or CYC-based regimens are used (7). Thus, even with new treatment options and refined CYC regimens designed to limit CYC exposure (8), disease relapses in AAV remain frequent and, consequently, so does the need for re-treatment.

With this high frequency of relapses, it is important to determine the optimal regimen for remission reinduction and maintenance therapy in AAV. Repeat administration of RTX is safe and effective in rheumatoid arthritis (9–11). Given its efficacy for induction of remission in AAV, repeat RTX administration may be effective in the treatment of disease relapses in these conditions. Indeed, the findings of several retrospective studies suggest that serial RTX use is well tolerated and effective in re-treating active disease and preventing disease relapses (12–15). However, no prospective evaluation of this strategy has been reported to date.

We report here prospective data on patients in the RAVE trial who were treated with RTX and glucocorticoids for severe disease relapse according to study protocol after initial successful remission induction. For patients who were randomized initially to receive RTX, this represented the second course of RTX.

PATIENTS AND METHODS

Study design and patients. Details on the RAVE trial design have been published previously (4,16). Briefly, the RAVE trial enrolled ANCA-positive patients with either GPA or MPA who met criteria for severe disease and had a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) (17) of >3 or 1 major disease item. Patients were assigned in a 1:1 manner to receive RTX followed by AZA placebo or CYC followed by AZA. Patients who experienced a severe relapse between months 6 and 18 (defined as a BVAS/WG of >3 or 1 major disease item or a relapse not meeting the above criteria but classified through investigator discretion as severe) were eligible to receive RTX on an open-label basis. Five patients with severe relapse between months 6 and 18 were not re-treated in the open-label regimen: 3 patients in the RTX group were treated according to the investigator's best medical judgment and 1 withdrew due to an adverse event, and 1 patient in the CYC/AZA group voluntarily withdrew from the study. Patients who experienced severe relapses before the 6-month time point (3 in the RTX group and 9 in the CYC/AZA group) were eligible for blinded crossover to the opposite treatment arm and were not included in this analysis; their outcomes have been reported previously (7). Patients with serum creatinine concentrations ≥4.0 mg/dl or diffuse alveolar hemorrhage requiring ventilatory support were excluded from enrollment in the RAVE trial but could receive open-label RTX at the discretion of the investigator if the event occurred after the 6-month time point.

Treatments. Patients initially randomized to the RTX treatment group received intravenous RTX (375 mg/m^2 once weekly for 4 weeks) plus daily placebo CYC followed by placebo AZA upon remission. Patients randomized to the CYC group received RTX placebo infusions and oral CYC (2 mg/kg, adjusted for renal insufficiency) for 3–6 months followed by AZA (2 mg/kg) for a total of 18 months of therapy. Both groups received glucocorticoids according to the same

Table 1. Baseline characteristics of the AAV patients receiving RTX for disease relapse*

	Re-treatment with RTX (initially randomized to RTX group) (n = 15)	First RTX course (initially randomized to CYC/AZA group) (n = 11)
PR3 ANCA positive	12 (80)	9 (82)
GPA	13 (87)	11 (100)
Relapsing disease at study entry	10 (67)	6 (55)
Received CYC prior to study entry	8 (53)	6 (55)
BVAS/WG at study entry, mean (range)	7.2 (4–13)	9.5 (3–16)
Time to initiation of open-label RTX, mean (range) days	381 (225–556)	319 (197–537)
BVAS/WG at initiation of open-label RTX, mean (range)	5.3 (3–11)	5.3 (2–12)
Not taking prednisone at time of relapse	10 (67)	8 (73)
Prednisone dosage at relapse, mean (range) mg/day	2.8 (0–15)	2.0 (0–10)
Prednisone dosage at relapse excluding patients not receiving prednisone (dosage 0), mean (range) mg/day	8.5 (3–15)	7.5 (5–10)
Organ involvement		
Constitutional signs or symptoms	10 (67)	6 (55)
Cutaneous involvement	1 (7)	2 (18)
Mucous membranes and eyes	1 (7)	0 (0)
Ear, nose, and throat	7 (47)	7 (64)
Pulmonary involvement	6 (40)	7 (64)
Nodules/cavities	3 (20)	1 (9)
Endobronchial involvement	0 (0)	4 (36)
Alveolar hemorrhage	1 (7)	2 (18)
Other	3 (20)	1 (9)
Renal involvement†	6 (40)	2 (18)
Hematuria	4 (27)	2 (18)
RBC casts	2 (13)	0 (0)
Increase in serum creatinine level	3 (20)	1 (9)
Serum creatinine, mean (range) mg/dl	1.3 (0.7–4.1)	1.2 (0.7–2.5)
Neurologic involvement	3 (20)	2 (18)

* Except where indicated otherwise, values are the number (%). AAV = antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; RTX = rituximab; CYC = cyclophosphamide; AZA = azathioprine; PR3 = proteinase 3; GPA = granulomatosis with polyangiitis (Wegener's); BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis.
† Severe renal disease was defined as the presence of red blood cell (RBC) casts or an increasing serum creatinine level.

protocol, which allowed for up to 3 gm of intravenous methylprednisolone (1 gm/day for 3 days) followed by prednisone 1 mg/kg/day. The prednisone was tapered to discontinuation over 5.5 months in all patients in whom remission was achieved and maintained.

Patients who experienced severe relapses between months 6 and 18 were eligible to receive RTX (375 mg/m^2 once weekly for 4 weeks) in conjunction with glucocorticoids on an open-label basis. Patients were eligible to receive pulse intravenous glucocorticoids for 1–3 days at the physician's discretion. Oral prednisone 1 mg/kg/day (not to exceed 80 mg/day) was then started, and was tapered and withdrawn over 5.5 months according to the same prespecified schedule used for initial remission induction. Investigators remained blinded with regard to the patients' initial treatment assignment at the time of re-treatment.

Assessments. Disease activity was assessed with the BVAS/WG. Disease damage was assessed with the Vasculitis Damage Index (VDI) (18). Patients were assessed at 1, 2, 4, 6, and 12 months after initiation of treatment with open-label RTX, then every 6 months until the trial's common closeout date. This assessment schedule was identical to the schedule followed at trial entry for the first 6 months.

ANCA measurements. ANCA type and titer were determined by enzyme-linked immunosorbent assay (ELISA) (19). ELISA kits were kindly donated by Euroimmun. All ANCA measurements were performed simultaneously on the same ELISA plate at a single laboratory. Increases in ANCA level were defined as a 2-fold increase from one measurement to another or an increase to at least 20 IU if the result of the prior assay was negative.

B cell kinetics. B cells were measured by 5-color flow cytometry in a commercial laboratory under contract with the Immune Tolerance Network. B cell depletion was defined as $<$10 CD19+ B cells/μl, and full reconstitution as $>$69 CD19+ B cells/μl or return to baseline. B cell counts of 10–68 CD19+ B cells/μl were categorized as detectable.

Outcome measures and disease relapses. The primary end point of the retreatment analysis was complete remission, as defined by a BVAS/WG of 0 with no prednisone treatment at any time following retreatment with RTX and glucocorticoids. Secondary outcome measures included remission (defined as a BVAS/WG of 0 at any point after RTX treatment), complete response (defined as a BVAS/WG of 0 with a prednisone dosage of $\leq$10 mg/day at any point after RTX treatment), and number of disease relapses (defined as an

increase in the BVAS/WG of ≥1 point). Severe relapses were defined as described above; relapses not meeting criteria for severe relapse were classified as limited.

Adverse events. Adverse events (AEs) were recorded, and were graded according to the National Cancer Institute Common Terminology Criteria (20).

Statistical analysis. Binary outcomes were compared by chi-square or Fisher's exact test, depending on the cell sizes. Continuous outcomes between and within treatment groups were compared by Wilcoxon's rank sum test and Wilcoxon's signed rank test, respectively. All statistical tests were 2-sided. *P* values less than 0.05 were considered significant. SAS version 9.1 was used for all statistical analyses.

RESULTS

Twenty-six patients received treatment with RTX for severe disease relapses between months 6 and 18. This represented the second course of RTX for 15 patients and the first course of RTX for 11.

Demographic and general disease characteristics. Baseline features of the 26 patients are shown in Table 1. Twenty-one of the patients (81%) were proteinase 3 (PR3) ANCA positive, and 24 (92%) had GPA. The proportion of patients who were PR3 ANCA positive and had GPA was similar to that in the overall trial patient population, in which 66% were PR3 ANCA positive ($P = 0.12$) and 75% had GPA ($P = 0.05$). Both PR3 ANCA positivity and the clinical diagnosis of GPA (which correlate highly with one another) are known to be associated with disease relapse (21), and it is therefore not surprising that the percentages of patients with these baseline characteristics were high in this study of patients needing re-treatment. Sixteen patients (62%) had relapsing disease at trial entry and 14 (54%) had received a course of CYC before entry, for an earlier period of active disease.

The mean BVAS/WG at the time of relapse leading to treatment with RTX was lower than the mean BVAS/WG for the same patient subset at trial entry (5.3 versus 8.2; $P < 0.001$). Five patients had a higher BVAS/WG at re-treatment than at trial entry. Eighteen patients were not receiving prednisone at the time of relapse, while the remaining 8 were receiving an average of 8.5 mg of prednisone daily (range 3–15). The mean time from the date of randomization to treatment or re-treatment with RTX for severe disease relapse was 355 days (319 days [range 195–537] in the CYC/AZA group and 381 days [range 225–556] in the RTX group). (Patients who experienced a relapse before month 6 were not eligible for open-label RTX and are not included in this analysis.) After receiving RTX for treatment of disease relapse, patients were followed up for a mean of 311 days (range 29–427). There were no significant differences in baseline characteristics between the patients in this cohort who were initially randomized to receive RTX and those initially randomized to receive CYC/AZA.

Re-treatment with RTX and prednisone. Fifteen patients initially randomized to the RTX group received RTX and prednisone (mean starting dosage 68 mg/day)

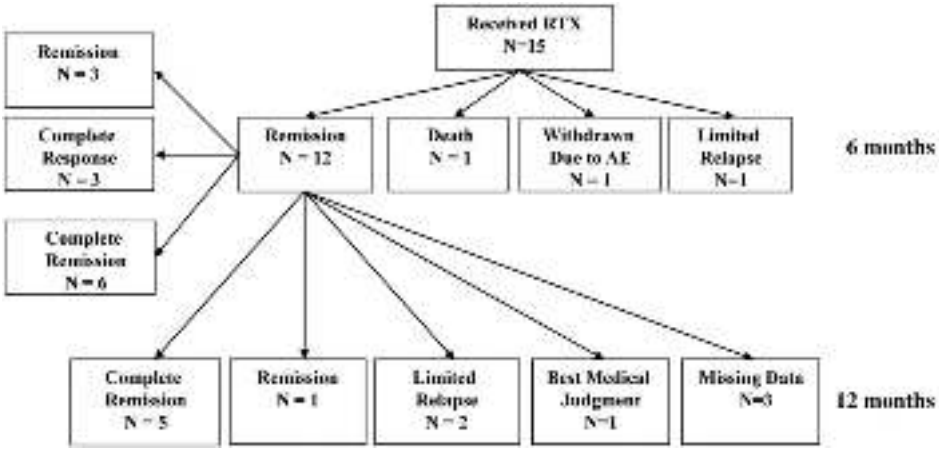

Figure 1. Outcomes in the patients with antineutrophil cytoplasmic antibody–associated vasculitis initially randomized to the rituximab (RTX) treatment group who subsequently received RTX for severe disease relapse. Remission was defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0, complete response as a BVAS/WG of 0 and prednisone dosage of ≤10 mg/per day, and complete remission as a BVAS/WG of 0 and no prednisone treatment. Missing Data refers to patients who did not have a 12-month visit but continued to be followed up in the study until the common closeout date.

Table 2. Outcomes in AAV patients receiving RTX for disease relapse*

	Re-treatment with RTX (initially randomized to RTX group) (n = 15)	First RTX course (initially randomized to CYC/AZA group) (n = 11)
Followup time after initiation of re-treatment, mean (range) days	302 (35–427)	324 (29–377)
Starting prednisone dosage to treat relapse, mean mg/day	67.8	69.1
Pulse methylprednisolone treatment		
1 pulse	11 (73)	6 (55)
2 pulses	0 (0)	1 (9)
3 pulses	1 (7)	2 (18)
Remission†	13 (87)	10 (91)
Time to remission, mean (range) days	56 (27–181)	36 (27–60)
Complete response‡	10 (67)	9 (82)
Time to complete response, mean (range) days	133 (95–186)	130 (112–182)
Complete remission§	6 (40)	7 (64)
Time to complete remission, mean (range) days	166 (121–184)	171 (124–189)
Limited relapses after initiation of re-treatment with RTX	3 (20)	1 (9)
Severe relapses after initiation of re-treatment with RTX	0 (0)	2 (18)
BVAS/WG at relapse after initiation of re-treatment with RTX, mean (range)	2.7 (2–3)	6 (1–11)
Time to relapse after initiation of re-treatment with RTX, mean (range) days	299 (121–428)	271 (121–364)
Baseline VDI	2.1 (0–7)	1.1 (0–5)
VDI at initiation of re-treatment with RTX	3.2 (0–8)	2.0 (0–6)
VDI at 12 months after initiation of re-treatment with RTX	4.6 (0–10)	3.7 (1–7)

* Except where indicated otherwise, values are the number (%). VDI = Vasculitis Damage Index (see Table 1 for other definitions).
† BVAS/WG score of 0.
‡ BVAS/WG score of 0 and prednisone dosage ≤10 mg/day.
§ BVAS/WG score of 0 and no prednisone treatment.

as a second treatment course during the study period. Outcomes in these patients at the 6- and 12-month time points after re-treatment are represented in Figure 1. Treatment with this regimen led to remission in 13 patients (87%), within a median of 30 days. In 10 of the 15 patients (67%), the prednisone dosage could be reduced to ≤10 mg/day after remission was achieved; in 6 of the 15, prednisone treatment could be discontinued completely (complete remission) (Table 2). Of the 2 patients in whom remission was not achieved, 1 died of progressive diffuse alveolar hemorrhage despite re-treatment with RTX. In the other, the BVAS/WG had improved to a score of 1 before a limited relapse occurred 12 months after re-treatment with RTX. Two patients experienced limited relapses after remission.

Treatment with RTX and prednisone after initial randomization to the CYC/AZA group. Outcomes in the 11 patients who were treated with RTX and prednisone for disease relapse following initial randomization to receive CYC/AZA treatment were similar to those who received RTX following initial assignment to the RTX group (Table 2 and Figure 2). Remission was achieved in 10 patients (91%), and complete remission in 7 (64%). Among these 11 patients treated with RTX for the first time, 3 experienced relapses, of which 2 were severe.

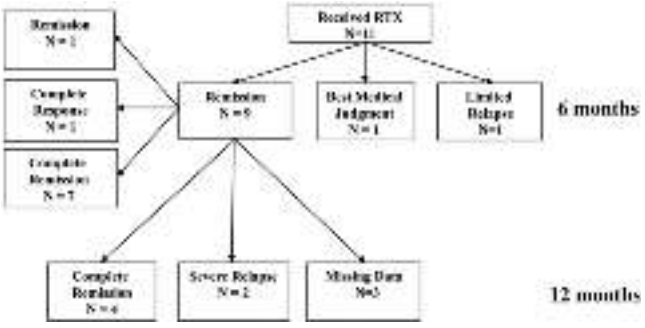

Figure 2. Outcomes in the patients with antineutrophil cytoplasmic antibody–associated vasculitis initially randomized to the cyclophosphamide/azathioprine treatment group who subsequently received rituximab (RTX) for severe disease relapse. Remission was defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0, complete response as a BVAS/WG of 0 and prednisone dosage of ≤10 mg/per day, and complete remission as a BVAS/WG of 0 and no prednisone treatment. Missing Data refers to patients who did not have a 12-month visit but continued to be followed up in the study until the common closeout date.

Table 3. ANCA and B cell status in AAV patients at the time of severe relapse and 6 months after initiation of re-treatment with RTX*

	Re-treatment with RTX (initially randomized to RTX group) (n = 15)	First RTX course (initially randomized to CYC/AZA group) (n = 11)
ANCA titer at severe relapse		
Increasing	12 (80)	8 (73)
Positive	1 (7)	1 (9)
Negative	2 (13)	2 (18)
ANCA titer 6 months after initiation of re-treatment		
Increasing	1 (7)	0 (0)
Positive	5 (33)	7 (64)
Negative	9 (60)	4 (36)
B cells at relapse leading to re-treatment		
Depleted	1 (7)	0 (0)
Detectable	3 (20)	5 (46)
Reconstituted	11 (73)	3 (27)
Missing data	0 (0)	3 (27)
B cells 6 months after initiation of re-treatment		
Depleted	10 (67)	8 (73)
Detectable	1 (7)	0 (0)
Reconstituted	1 (7)	2 (18)
Missing data	3 (20)	1 (9)

* Values are the number (%). See Table 1 for definitions.

ANCA and B cell levels at relapse and after re-treatment with RTX. At the time of severe relapse that led to treatment with open-label RTX, 20 patients (77%) had increasing ANCA titers, 2 patients had persistently positive ANCA, and 4 patients were ANCA negative. Twenty-two of 23 patients with samples collected at the time of relapse (96%) had detectable or reconstituted B cells (Table 3). The patient who died due to progressive alveolar hemorrhage had both detectable B cells and an increasing ANCA titer at the time of disease relapse. Only 1 patient was both negative for ANCA and had depleted B cells. Of the 6 patients who experienced a flare after re-treatment with open-label RTX, only 1 had depleted B cells at the time of re-treatment.

Although these data might suggest that measurement of B cell concentrations and ANCA titers is useful in predicting disease flares in AAV, they must be contrasted with the number of patients in the RAVE trial overall who had detectable B cells and positive ANCA titers after remission but did not experience flares during the course of followup. Two-thirds of the patients in the RTX group had detectable or reconstituted B cells without experiencing a relapse up to the 18-month time point (with more prolonged B cell depletion in the CYC/AZA group). Similarly, two-thirds of the patients in both groups had a positive or increasing ANCA titer without experiencing a relapse within 18 months of trial entry (21).

Six months after re-treatment with RTX, B cells remained depleted in 18 of 22 patients (82%) (data missing on 4 patients). There were no significant differences between patients receiving their first or second course of RTX with respect to B cell depletion or reconstitution following RTX treatment. ANCA had become negative at 6 months after re-treatment in 13 patients (9 who initially received RTX, 4 who initially received CYC/AZA; $P = 0.43$).

Adverse events in patients treated with RTX and prednisone for disease relapse. There were a total of 156 AEs in patients who received open-label RTX for severe disease relapse (Table 4). Eighty-five of the events occurred in 14 patients receiving a second course of RTX, and 71 in 9 patients receiving a first course of RTX. Compared to all patients during the initial 6 months of the trial, there were fewer AEs during the first 6 months after re-treatment in patients who were re-treated with RTX for disease relapse (8.4 per patient-year versus 24.1 per patient-year; $P < 0.001$). This difference persisted until the end of followup after re-treatment (4.7 AEs per patient-year, compared to 11.8 AEs per patient-year 18 months after initial randomization; $P < 0.001$). There was only 1 episode of grade 1 leukopenia and no cases of severe neutropenias

Table 4. Adverse events among AAV patients after initiation of RTX for disease relapse*

	Grade 1 AEs	Grade 2 AEs	Grade 3 AEs	Grade 4 AEs	Death	Total
No. of AEs at 6 months among patients receiving RTX	78	18	5	0	1	102
No. of AEs per patient-year at 6 months among patients receiving RTX	6.4	1.5	0.4	0	0.1	8.4
No. of AEs at end of followup among patients receiving RTX	113	34	8	0	1	156
No. of AEs per patient-year at end of followup among patients receiving RTX	3.4	1.0	0.2	0	0.0	4.7
No. of AEs at 6 months among all patients in the RAVE trial	1,404	316	88	11	3	1,822
No. of AEs per patient-year at 6 months among all patients in the RAVE trial	18.5	4.2	1.2	0.1	0.0	24.1
No. of AEs at 18 months among all patients in the RAVE trial	1,809	429	111	12	3	2,364
No. of AEs per patient-year at 18 months among all patients in the RAVE trial	9.0	2.1	0.6	0.1	0.0	11.8

* AEs = adverse events; RAVE trial = Rituximab in AAV trial (see Table 1 for other definitions).

reported in this cohort. There were 13 infections, 10 (77%) of which involved the ears, nose, and upper respiratory tract. Other infections included viral gastroenteritis, influenza, and a urinary tract infection (1 each). There were 2 infections of grade 3 severity (gastroenteritis and sinusitis).

Disease damage in patients treated with RTX and prednisone for disease relapse. Average VDI scores increased in both treatment groups over the course of the study. In patients initially randomized to the RTX group, the mean VDI rose from 2.1 at study entry to 3.2 at re-treatment with RTX and 3.9 at the end of followup. Similarly, in patients initially randomized to the CYC/AZA group, the VDI rose from 1.1 at study entry to 2.0 at re-treatment with RTX and 2.8 at the end of followup. The increase in the VDI was attributable to both direct disease damage and glucocorticoid-related toxicity (data not shown).

DISCUSSION

We have analyzed outcomes in AAV patients in the RAVE trial who were treated with RTX and prednisone for disease relapse. Our results demonstrate that a majority of patients who received a second course of RTX and prednisone achieved clinical remission without an increase in the number of adverse events compared to patients in the RAVE trial overall. This is the first reported prospective study to date on the repeat use of RTX in patients with AAV who experience disease relapses.

The prospective design of this study and the collection of data within the confines of a label-enabling clinical trial offer certain advantages over retrospective examinations of serial RTX treatment (11–14). First, patients in the RAVE trial were re-treated with RTX only for severe relapses of the underlying disease, and the definitions of remission, complete remission, and severe and limited disease relapses were specified in advance in the protocol. In contrast, a significant proportion of patients in the retrospective studies received RTX on a scheduled basis (every 4 or 6 months) regardless of the presence or absence of AAV symptoms (11,12). Second, no concomitant immunosuppression treatment aside from prednisone was allowed in our trial. In comparison, in most retrospective studies of serial RTX treatment (11,12,14), concomitant immunosuppressive medications in addition to glucocorticoids were allowed during at least a portion of the study, making it difficult to ascertain the impact of RTX and prednisone.

The rate of remission after a second course of RTX (87%) in our cohort compares favorably to the remission rate observed with initial use of RTX for remission induction in the RAVE trial (86%) and with remission rates in retrospective studies of serial RTX treatment. The 87% number also compares favorably to historical success rates in induction of remission in AAV (5,22–24). Numerically more subjects initially randomized to the CYC/AZA group achieved complete remission after re-treatment with RTX as compared to those initially randomized to the RTX group and then re-treated (7 of 11 [64%] versus 6 of 15 [40%]; $P = 0.42$), but time to remission and relapse rates were similar between the 2 groups. This suggests that the safety and

efficacy of re-treatment with RTX is not dependent on whether prior treatments included RTX or CYC-based therapy.

ANCA titers and B cell counts did not predict disease relapse in this cohort. Even though most patients had a positive or increasing ANCA titer and detectable or reconstituted B cells at the time of relapse, two-thirds of patients in the RAVE trial with positive ANCA or detectable B cells did not experience a relapse during the first 18 months of the study. Thus, the return of B cells and the presence of a positive or increasing ANCA titer does not signal an imminent disease flare in the majority of patients. Conversely, relapse was unlikely in patients who were negative for ANCA and had depleted B cells between the 6- and 18-month time points (21). Prior to the 6-month time point, however, the occurrence of disease relapses in the setting of ANCA negativity and depleted B cells is not uncommon (7).

We observed a lower rate of AEs among patients after treatment of relapse with RTX than was found in the RAVE trial overall (4.7 and 11.8 adverse events per patient-year, respectively). One possible explanation for this is that the rate of AEs is related to disease severity rather than to treatment, as patients treated with RTX for disease relapse had lower disease activity scores at the time of re-treatment compared to study entry. Late-onset neutropenia has been reported after treatment with RTX (25), but was not observed in this study. Infections following re-treatment with RTX most frequently had viral etiologies and were primarily only mild to moderate in severity.

Disease damage as measured by the VDI continued to increase throughout the study in patients treated with RTX for disease relapse. This was attributable to disease activity (e.g., hearing loss, peripheral neuropathy) and glucocorticoid-related toxicity (e.g., osteoporosis, hypertension, and diabetes, among others). A detailed analysis of disease damage in the RAVE trial is currently under way. The progression of damage as measured by the VDI throughout this trial raises the important question of whether progressive damage in AAV might be halted by regularly scheduled re-treatment with RTX instead of waiting for the occurrence of clinically evident disease relapse before RTX is reinstituted.

Our study has several limitations. The majority of the patients treated with RTX for disease relapse were positive for PR3 ANCA. Thus, generalizability of these findings to patients with MPO ANCA is unclear. However, the data we are able to provide on PR3 ANCA–positive patients address the patient subset that is most likely to experience disease relapses and is therefore the subset for whom re-treatment with RTX is most important to consider. Patients experiencing a disease relapse after initial achievement of remission were not randomized to different treatment approaches in our study, and therefore there was no true comparison group for patients re-treated with RTX. However, we attempted to provide a measure of comparison by examining patients who received RTX for the first time after initial randomization to CYC/AZA treatment. There remains some concern in the literature regarding the possibility of hypogammaglobulinemia following serial RTX treatment. We did not address this in the present report because a complete analysis of hypogammaglobulinemia in the RAVE trial is currently under way. Because the regimen used in the trial consisted of 4 weekly 375-mg/m^2 doses of RTX, our results are not necessarily generalizable to the regimen of 1 gm administered twice that is commonly used in rheumatoid arthritis, even though these 2 regimens appear to be approximately equivalent in their ability to deplete circulating B cells (10). Finally, the sample size of patients with disease relapses who received RTX is small, limiting subgroup comparison and detection of rare events.

In conclusion, this first prospective analysis of the re-treatment of AAV patients who are experiencing disease relapse appears to confirm observations from retrospective studies that re-treatment with RTX and glucocorticoids is safe and effective in this setting. Studies to compare strategies consisting of "on-demand" treatment with RTX versus scheduled RTX in AAV are warranted. Further insights into the pathophysiology of AAV, identification of better biomarkers, and a more complete understanding of which patients are at risk for relapse and the timing of such relapses may lead to rational applications of B cell depletion therapy as prophylactic treatment of this disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Specks, Merkel, Seo, Spiera, Langford, Hoffman, Kallenberg, St.Clair, Tchao, Viviano, Ding, Iklé, Brunetta, Allen, Geetha, Stegeman, Stone.

Acquisition of data. Specks, Merkel, Seo, Spiera, Langford, Hoffman, Kallenberg, St.Clair, Tchao, Viviano, Ding, Iklé, Allen, Fervenza, Geetha, Keogh, Kissin, Peikert, Stegeman, Ytterberg, Stone.

Analysis and interpretation of data. Miloslavsky, Specks, Merkel, Seo, Spiera, Langford, Hoffman, Kallenberg, St.Clair, Tchao, Viviano, Ding, Iklé, Villarreal, Jepson, Brunetta, Geetha, Monach, Stone.

ROLE OF THE STUDY SPONSOR

Genentech and Biogen Idec provided the study medications for the RAVE Trial and reviewed the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Genentech or Biogen Idec.

ADDITIONAL DISCLOSURES

Dr. Iklé, Mr. Villarreal, and Mr. Jepson are employed by Rho, a contract research organization.

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