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Outcomes of Nonsevere Relapses in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis Treated With Glucocorticoids

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Objective. **Nonsevere relapses are more common than severe relapses in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), but their clinical course and treatment outcomes remain largely unexamined. We undertook this study to analyze the outcomes of patients with nonsevere relapses in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial who were treated with prednisone according to a prespecified protocol.**

Methods. **RAVE was a randomized, double-blind, placebo-controlled trial comparing rituximab (RTX) to cyclophosphamide (CYC) followed by azathioprine (AZA) for induction of remission. Patients who experienced nonsevere relapses between months 1 and 18 were treated with a prednisone increase without a concomitant change in their nonglucocorticoid immunosuppressants, followed by a taper.**

Results. **Forty-four patients with a first nonsevere relapse were analyzed. In comparison to the 71 patients who maintained relapse-free remission over 18 months, these patients were more likely to have proteinase 3–ANCAs, diagnoses of granulomatosis with polyangiitis (Wegener's), and a history of relapsing disease at baseline. A prednisone increase led to remission in 35 patients (80%). However, only 13 patients (30%) were able to maintain second remissions through the followup period (mean 12.5 months); 31 patients (70%) had a second disease relapse, 14 of them with severe disease. The mean time to second relapse was 9.4 months (4.7 months in the group treated with RTX versus 13.7 months in the group treated with CYC/AZA; $P < 0.01$). Patients who experienced nonsevere relapses received more glucocorticoids than those who maintained remission (6.7 grams versus 3.8 grams; $P < 0.01$).**

Conclusion. **Treatment of nonsevere relapses in AAV with an increase in glucocorticoids is effective in restoring temporary remission in the majority of patients, but recurrent relapses within a relatively short interval remain common. Alternative treatment approaches are needed for this important subset of patients.**

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Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) are the major forms of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV). Most patients with AAV achieve at least temporary disease remission with induction regimens based on cyclophosphamide (CYC), rituximab (RTX), or methotrexate (MTX) (1–4). However, subsequent disease relapses occur in more than one-half of patients during long-term followup (5–7). The majority of such relapses are not severe and do not pose immediate threats either to major organ function or to the patient's life (2,8,9). Despite reports from some clinical trials that nonsevere disease relapses are 3 times more common than severe relapses (2), the clinical course, treatment outcomes, and ultimate implications of such disease relapses remain largely unexamined. Previous prospective trials have not provided the outcomes of nonsevere relapses (1,2,4,5), have not differentiated between severe and nonsevere relapses (10,11), or have not considered patients with 1 or 2 recurrent nonsevere manifestations of active disease to have experienced a relapse (8,9). Moreover, the terminology and definitions of nonsevere relapses have varied over the past decades, further complicating the interpretation of clinical studies (12,13).

We examined the outcomes of patients with nonsevere relapses in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial who were treated according to a uniform protocol. The protocol consisted of a glucocorticoid increase selected at the discretion of the investigator, followed by a defined taper, without a change in nonglucocorticoid immunosuppressants.

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PATIENTS AND METHODS

RAVE trial. Details of the RAVE trial design was previously reported (3,14). ANCA enzyme-linked immunosorbent assay kits were provided by Euroimmun. The trial enrolled ANCA-positive patients with GPA or MPA who had severe disease (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis [BVAS/WG] of >3, or one major item) (15). Patients were assigned to 1 of 2 treatment groups: either CYC (2 mg/kg, adjusted for renal insufficiency) for 3–6 months followed by azathioprine (AZA) (2 mg/kg) for a total of 18 months; or RTX (4 weekly infusions of 375 mg/m^2) followed by placebo. Both groups received the same glucocorticoid protocol, tapered to discontinuation by 6 months.

Remission was defined as a BVAS/WG of 0, and complete remission was defined as a BVAS/WG of 0 with discontinuation of glucocorticoids. The results of the trial's primary outcomes (the percentages of patients who achieved and maintained complete remission at 6 and 18 months without additional changes in therapy) have been reported (3,16).

Analysis of nonsevere relapses. Patients who had an increase in the BVAS/WG of ≤3 and the absence of major BVAS/WG items between months 1 and 18 were included in the analysis. Three patients who had BVAS/WG of 4 at relapse were also included because their relapses were considered nonsevere by their treating physicians. The disease exacerbations analyzed included "relapses" (n = 40), defined as an increase in the BVAS/WG following the achievement of remission, and "flares" (n = 4), defined as an increase in the BVAS/WG before achieving remission. For the purposes of this report, we refer to both "relapses" and "flares" as relapses. Severe relapses were defined as recurrent AAV activity that would have been treated with CYC plus high-dose glucocorticoids under the standard of care that existed at the time the trial began. Patients who had a change in their initially assigned treatment prior to their first nonsevere relapse (e.g., crossover to the opposite treatment arm due to a severe relapse) were excluded from the analysis in order to limit the effects of previous therapy on the outcomes of treatments that followed first nonsevere relapses.

Treatments and followup. Patients with nonsevere relapses between months 1 and 18 were treated by increasing prednisone to a dose selected at the discretion of the investigator. The new dosage was maintained for 1 month before resumption of a specified taper every 2 weeks, as follows: 60 mg/day, 40 mg/day, 30 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day, and 2.5 mg/day. In order to study clinical events after the first nonsevere relapse, patients' outcome data were analyzed until one of the following occurred: a severe relapse, a second nonsevere relapse, a change in nonglucocorticoid immunosuppressants, withdrawal from the trial, or the common closeout date.

Statistical analysis. Binary outcomes were compared using the chi-square test or Fisher's exact test. Continuous outcomes between treatment arms were compared using the Wilcoxon rank sum test. Wald confidence intervals of 95% were calculated for differences in outcomes between treatment arms at the different time points. The data sets for these analyses are accessible through TrialShare (https://www.itntrialshare.org), a publicly accessible web site developed by the Immune Tolerance Network.

RESULTS

Numbers of nonsevere relapses. Sixty-seven nonsevere relapses occurred in 51 patients between months

Table 1. Characteristics of the patients with nonsevere relapse of disease*

	RTX-treated patients (n = 23)	CYC/AZA-treated patients (n = 21)	All patients (n = 44)
Male	12 (52)	9 (43)	21 (48)
PR3-ANCAs	18 (78)	18 (86)	36 (82)
GPA	20 (87)	20 (95)	40 (91)
Relapsing disease at study entry	15 (65)	13 (62)	28 (64)
Time to first nonsevere relapse, mean (range) months†	7.7 (1.8–15.1)	7.3 (2.4–16.9)	7.5 (1.8–16.9)
Achieved remission before relapse	20 (87)	20 (95)	40 (91)
BVAS/WG at relapse, mean	1.8	1.6	1.7
Not receiving prednisone at relapse	14 (61)	14 (67)	28 (64)
Prednisone dosage at relapse, median (range) mg/day‡	5.0 (2.5–20)	5.0 (2.5–15)	5.0 (2.5–20)
Organ involvement			
Constitutional features§	18 (78)	11 (52)	29 (66)
Cutaneous involvement	2 (9)	1 (5)	3 (7)
Mucous membranes and eyes	2 (9)	5 (24)	7 (16)
Mouth ulcers	1 (4)	0 (0)	1 (2)
Conjunctivitis/episcleritis	0 (0)	5 (24)	5 (11)
Other	1 (4)	0 (0)	1 (2)
Ear, nose, and throat	7 (30)	4 (19)	11 (25)
Bloody nasal discharge	3 (13)	2 (10)	5 (11)
Sinus involvement	2 (9)	2 (10)	4 (9)
Other	2 (9)	1 (5)	3 (7)
Pulmonary involvement	5 (22)	3 (14)	8 (18)
Nodules/cavities	2 (9)	1 (5)	3 (7)
Endobronchial involvement	0 (0)	2 (10)	2 (5)
Other	3 (13)	1 (5)	4 (9)
Renal involvement (hematuria)	1 (4)	3 (14)	4 (9)
Other minor items	2 (9)	0 (0)	2 (5)

* Except where indicated otherwise, values are the number (%). RTX = rituximab; CYC/AZA = cyclophosphamide/azathioprine; PR3-ANCAs = antineutrophil cytoplasmic antibodies with specificity for proteinase 3; GPA = granulomatosis with polyangiitis (Wegener's); BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis.
† Of the 4 patients who had disease flares before achieving remission, those flares occurred 1.8 months (n = 1), 2.4 months (n = 1), and 3.9 months (n = 2) after study entry.
‡ If dosage >0 mg/day.
§ Fevers, arthritis/arthralgias.

Table 2. Comparison of baseline characteristics in the patients with nonsevere relapse of disease and in the patients who achieved and maintained remission through 18 months*

	Had nonsevere relapse of disease (n = 44)	Achieved and maintained remission through 18 months (n = 71)	*P*
GPA	40 (91)	50 (70)	<0.01
MPA	4 (9)	21 (30)	
PR3-ANCAs	36 (82)	43 (61)	<0.02
MPO-ANCAs	8 (18)	28 (39)	
Relapsing disease	28 (64)	29 (41)	<0.02
New diagnosis	16 (36)	42 (59)	
GPA and PR3-ANCAs and relapsing disease	24 (55)	21 (30)	<0.01
Fewer than all 3 factors†	20 (45)	50 (70)	

* Values are the number (%). GPA = granulomatosis with polyangiitis (Wegener's); MPA = microscopic polyangiitis; PR3-ANCAs = antineutrophil cytoplasmic antibodies with specificity for proteinase 3; MPO-ANCAs = ANCAs with specificity for myeloperoxidase.
† Patients who had 0, 1, or 2 of the 3 risk factors (GPA, PR3-ANCAs, relapsing disease).

Table 3. Outcome after first nonsevere relapse of disease*

	RTX-treated patients (n = 23)	CYC/AZA-treated patients (n = 21)	All patients (n = 44)
Followup until next event, mean (range) months†	7.8 (0.7–28.3)	17.6 (1.4–39.2)‡	12.5 (0.7–39.2)
Prednisone dose for treatment of relapse, median (range) mg/day	11 (2.5–80)	20 (4–60)	17.5 (2.5–80)
Achieved remission	17 (74)	18 (86)	35 (80)
Time to remission, mean (range) months	2.2 (0.5–4.4)	2.8 (0.9–4.2)	2.5 (0.5–4.4)
Achieved complete remission§	7 (30)	11 (52)	18 (41)
Time to complete remission, mean (range) months	3.9 (1.9–6.8)	6.1 (2.1–12.5)	5.3 (1.9–12.5)
Outcome at end of followup			
Nonsevere relapse	10 (44)	7 (33)	17 (39)
Severe relapse	5 (22)	9 (43)	14 (32)
Maintained remission until censoring	4 (17)	0 (0)	4 (9)
Maintained remission until common closeout date	4 (17)	4 (19)	8 (18)
Data not available at time of censoring	0 (0)	1 (5)	1 (2)
Time to second relapse, mean (range) months	4.7 (0.7–17.6)	13.7 (1.4–37.2)‡	9.4 (0.7–37.2)
Not receiving prednisone at second relapse	5 (22)	10 (48)	15 (41)
Prednisone dosage at second relapse, median (range) mg/day¶	7.5 (2.5–20)	7.5 (5–10)	7.5 (2.5–20)

* Except where indicated otherwise, values are the number (%). CYC/AZA = cyclophosphamide/azathioprine.
† The next event was defined as a severe relapse, a second nonsevere relapse, a change in nonglucocorticoid immunosuppressants (which could occur at the 18-month time point according to the investigator's best medical judgment), withdrawal from the trial, or the common closeout date.
‡ $P < 0.01$ versus rituximab (RTX)–treated patients.
§ Of the 4 patients who had a nonsevere flare before achieving disease remission, all 4 achieved remission and 1 had a subsequent severe flare.
¶ If dosage >0 mg/day.

1 and 18, compared with a total of 45 severe relapses in 41 patients. After excluding 7 patients who did not continue their originally assigned treatment, 44 patients were analyzed (23 in the group receiving RTX, 21 in the group receiving CYC/AZA) ($P = 0.76$).

Patient characteristics at first nonsevere relapse. Thirty-six patients (82%) were proteinase 3 (PR3)–ANCA positive and 40 (91%) had GPA (Table 1). Twenty-eight patients (64%) had relapsing disease at study entry. Compared to the subset of patients who achieved and maintained disease remission through 18 months of followup (n = 71), patients who experienced nonsevere relapses had significantly more frequent PR3-ANCA positivity at baseline, GPA diagnosis, and history of relapsing disease (Table 2). Among the 44 patients with nonsevere relapses, 24 (55%) had all 3 of these characteristics as compared to 30% of the patients who maintained disease remission ($P < 0.01$).

Forty of 44 patients (91%) achieved remission (BVAS/WG of 0) before experiencing their first nonsevere relapse, which occurred on average 7.5 months (range 1.8–16.9 months) after study entry (7.7 months in the group receiving RTX versus 7.3 months in the group receiving CYC/AZA; $P > 0.99$). Sixteen of 44 patients (36%) were still receiving prednisone at the time of their first relapse (median 5.0 mg/day, range 2.5–20.0). Of the 21 patients in the group receiving CYC/AZA, 2 were receiving CYC at the time of relapse. Thirty-three patients had ANCAs measured at the first nonsevere relapse, and 32 had B cells measured. Ten patients (30%) were negative for ANCAs (30% in the group receiving RTX, 31% in the group receiving CYC/AZA) and 14 patients (44%) had undetectable B cells (45% in the group receiving RTX, 42% in the group receiving CYC/AZA). Five of 32 patients (16%) were both negative for ANCAs and had undetectable B cells at relapse.

The most common manifestations of nonsevere relapses were constitutional symptoms; ear, nose, and throat findings; ocular disease; and pulmonary involvement. Only 4 relapses (9%) were characterized by active kidney disease (hematuria in 4 patients, red blood cell casts in 1 patient). No patient had an increase in the serum creatinine level of >30%.

Treatment of first nonsevere relapse. After the first nonsevere disease relapse, patients' data were analyzed over a mean of 12.5 months (range 0.7–39.2 months) (7.8 months in the group receiving RTX versus 17.6 months in the group receiving CYC/AZA; $P < 0.01$) until a recurrent relapse, a change in nonglucocorticoid immunosuppressants, or the occurrence of the last study visit, whichever came first. An increase in prednisone led to remission in 35 of 44 patients (80%) (17 of 23 patients in the group receiving RTX [74%] versus 18 of 21 patients in the group receiving CYC/AZA [86%]; $P = 0.46$) (Table 3). The median prednisone dosage used to treat nonsevere relapses was 17.5 mg/day (range 2.5–80) (11 mg/day in the group receiving RTX, 20 mg/day in the group receiving CYC/AZA). However, disease remained in remission in only 13 patients

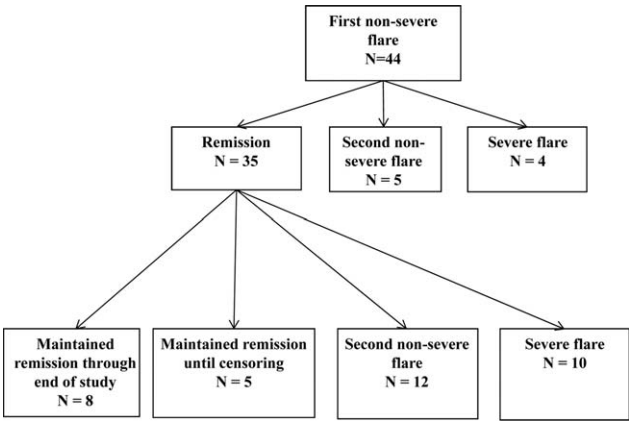

Figure 1. Outcomes in the patients with nonsevere relapses who were treated with glucocorticoids.

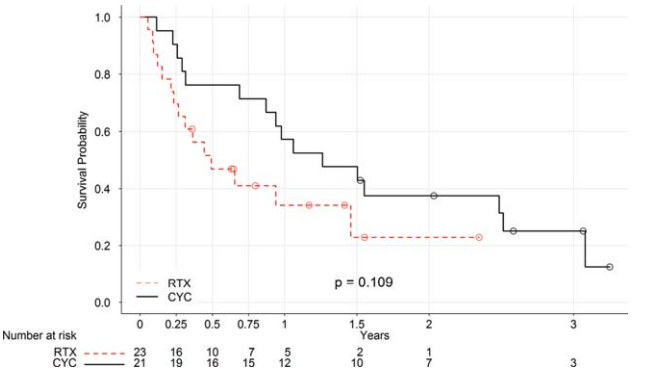

Figure 2. Relapse-free survival after initial nonsevere relapse. RTX = rituximab; CYC = cyclophosphamide.

(30%) (8 in the group receiving RTX, 5 in the group receiving CYC/AZA) until the conclusion of followup (Figure 1). The remaining patients had second relapses (Figure 2). Of the 13 patients whose disease remained in remission, 5 were censored at the 18-month time point because they were started on an additional immunosuppressive medication at the discretion of their treating physician (4 in the group receiving RTX added AZA, and 1 in the group receiving CYC/AZA added RTX).

The dose of prednisone used to treat the first nonsevere relapse did not appear to influence patient outcomes (Table 4). A similar percentage of patients achieved remission and maintained remission when treated with high-dose prednisone (≥20 mg/day) as opposed to low-dose prednisone (<20 mg/day). Seventy-seven percent of the patients with relapsing disease who were treated with high-dose prednisone achieved remission, and 23% of those patients maintained those remissions for the remainder of followup. In comparison, 82% of the patients with relapsing disease who were treated with low-dose prednisone achieved remission, and 36% maintained those remissions. A patient's likelihood of maintaining remission did not differ according to ANCA type (10 of 36 patients with PR3-ANCAs [28%] versus 3 of 8 patients with myeloperoxidase [MPO]–ANCAs [38%]; $P = 0.68$). Of the 4 patients with MPA, 3 had disease that remained in remission and 1 had a severe relapse of disease.

Characteristics of second relapses following first nonsevere relapses. Of the 31 patients who were not able to achieve and maintain remission throughout the followup period, 17 experienced a second nonsevere relapse (10 in the group receiving RTX, 7 in the group receiving CYC/AZA) and 14 experienced a severe relapse (5 in the group receiving RTX, 9 in the group receiving CYC/AZA). There were no differences in baseline characteristics or organ involvement at the first relapse between patients whose second relapse was severe and those whose second relapse was nonsevere (data not shown). Furthermore, the prednisone dose used to treat the first relapse did not appear to affect the likelihood that a second relapse would be severe. Thirty-six percent

Table 4. Outcomes by dose of prednisone used to treat first nonsevere relapse of disease*

	High-dose prednisone (n = 22)	Low-dose prednisone (n = 22)
BVAS/WG at first relapse, mean ± SD	2.0 ± 1.1	1.4 ± 0.73†
Achieved remission	17 (77)	18 (82)
Time to remission, mean (range) months	2.5 (0.5–4.1)	2.5 (1.0–4.4)
Achieved complete remission	8 (36)	10 (46)
Time to complete remission, mean (range) months	6.2 (3.3–12.5)	4.5 (1.9–9.7)
Outcome at end of followup		
Nonsevere relapse	8 (36.4)	9 (40.9)
Severe relapse	9 (40.9)	5 (22.7)
Time to second relapse, mean (range) months	9.9 (0.7–30.3)	8.7 (1.9–37.2)

* High-dose prednisone was defined as ≥20 mg/day, and low-dose prednisone was defined as <20 mg/day. Except where indicated otherwise, values are the number (%). BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis.
† $P = 0.05$ versus high-dose prednisone group.

of patients treated with high-dose prednisone experienced a second nonsevere relapse compared to 41% of those treated with low-dose prednisone. Forty-one percent of patients treated with high-dose prednisone experienced a severe relapse compared to 23% of those treated with low-dose prednisone. The mean time to second relapse was 9.4 months following the initial relapse (4.7 months in the group receiving RTX versus 13.7 months in the group receiving CYC/AZA; $P < 0.01$). Sixteen of the 31 patients (52%) were still receiving prednisone at the time of second relapse (median 7.5 mg/day, range 2.5–20). Of the 25 patients in whom ANCAs and B cells were measured at the time of their second relapses, ANCAs were present or increasing in 21 (84%) and B cells were detectable or reconstituted in 21 (84%). Only 1 patient had no ANCAs and undetectable B cells at the time of second relapse.

Cumulative prednisone doses and adverse events. Patients who had a nonsevere relapse had a greater mean cumulative prednisone dose over the first 18 months of the trial compared to patients who reached the primary end point (6.7 grams versus 3.8 grams; $P < 0.01$). Through the 18-month time point, there were no differences in adverse events between patients who experienced nonsevere relapses and those who achieved the primary end point (0.94 events per patient-year and 0.91 events per patient-year, respectively; $P = 0.08$). There were 5 severe infections among the 44 patients with disease relapse and 8 among the 71 patients who reached the primary end point. Damage, as measured by the Vasculitis Damage Index (VDI) (17), increased from trial entry to the first nonsevere relapse and again at the end of followup (mean values of 1.2, 1.6, and 2.3, respectively). However, the mean VDI increased at a similar rate for patients who reached the primary end point at 18 months (from 1.0 to 2.1) ($P = 0.99$).

DISCUSSION

Despite an expansion of the options for induction-of-remission regimens in AAV over the past 2 decades, disease relapses remain a therapeutic challenge. Our report is the first in which the outcomes of patients with nonsevere relapses are described. Although 80% of patients achieved remission after an increase in their prednisone dose, 70% of those patients went on to experience a second relapse, either nonsevere or severe, within an average of 6 months. Only 13 patients (30%) were able to maintain disease-free remissions until the end of followup, and only 8 (18%) were able to do so until their last study visit. These findings identify an important subset of patients with AAV who are unable to maintain prolonged remission and, as a result, receive higher doses of glucocorticoids. Such patients are more likely to have GPA, be PR3-ANCA positive, and have relapsing disease.

Because patients with nonsevere relapses constitute an important clinical subset, our definition of nonsevere relapse should be considered in the context of terminology previously used to characterize nonsevere AAV. Carrington and Liebow first used the term "limited Wegener's granulomatosis" to describe GPA that primarily involved the lungs as opposed to the kidneys (12). In 1992, Hoffman et al reported on the use of MTX and glucocorticoids in GPA patients with mild renal involvement, and such patients were also classified as having "limited" GPA (18). Several other studies also used this nomenclature (4,6,19). Thus, "limited" GPA has often been defined more broadly (particularly in the US) as disease activity that does not pose immediate threats either to major organ function or to the patient's life and that does not require treatment with CYC (2).

Several other terms have been used to describe nonsevere relapses. The European Vasculitis Study Group has used the terms "localized" to define disease confined to the upper or lower respiratory tract without constitutional symptoms and "early systemic" disease to define AAV without progressive end-organ damage and with creatinine concentrations of <120 μmoles/liter (1.35 mg/dl) (13). The "localized" and "early systemic" designations correspond approximately to the "limited" category. Finally, the term "minor relapse" has been used with widely varying definitions in a number of clinical trials, ranging from the occurrence of any BVAS item to the presence of at least 3 BVAS items (8–10).

Our prespecified definition of "nonsevere" relapse attempts to account for differences in previously used terminology by defining such relapses generally as those with the occurrence of any new disease activity, a BVAS/WG of ≤ 3, and no major BVAS/WG items. We propose that nonsevere relapses be defined in future trials as any new disease activity that does not include a major BVAS/WG item. A standard definition of nonsevere flare would facilitate understanding of the clinical course and treatment response in this important patient subgroup. Whether a strict BVAS/WG of ≤ 3 should also be added to the definition to increase standardization further is uncertain, as some patients with a higher BVAS/WG may be considered by some experts to have nonsevere disease, as was the case for 3 patients in this study. It should be noted that disease manifestations that qualify for a "nonsevere" designation may have a profound impact on patients' prognosis and quality of life. For example, orbital pseudotumors and subglottic stenoses are features of "limited" or "localized" disease,

yet they often lead to irreversible damage and substantial morbidity.

The high rate of second relapses observed in this subgroup of patients suggests a need for a treatment paradigm different from that used in the RAVE trial. Although prednisone was effective in reinducing remission in 80% of cases, the majority of patients treated in this manner did not sustain remission after prednisone had been tapered to a lower dose. In clinical practice, an addition or increase in the dose of AZA or MTX has been the standard of care for such disease relapses. B cell depletion may also be a viable approach in such patients (20,21). The recently reported trial of RTX versus AZA for maintenance in AAV (MAINRITSAN) demonstrated that RTX in combination with glucocorticoids was superior to AZA for prevention of disease relapses, suggesting that alternative regimens for maintenance of disease remission should be considered in AAV (21). The optimal method for remission induction and maintenance in this setting needs to be evaluated further in clinical trials.

Time to second relapse was shorter in RTX-treated patients than in CYC/AZA-treated patients (4.7 months versus 13.7 months; $P < 0.01$). A possible explanation is that patients who were randomly assigned to receive RTX received placebo rather than AZA after achieving remission. Only 4 patients in the RTX-treated group had undetectable B cells at relapse, suggesting that the major effects of RTX had waned by the time of disease relapse. Despite this treatment difference, neither the rates of subsequent relapses nor patients' ability to achieve or maintain remission after a first nonsevere relapse differed between the CYC/AZA-treated and RTX-treated groups.

Our results suggest that AZA may prolong time to relapse in patients who have had a previous relapse, but the efficacy of AZA in preventing disease relapses altogether, particularly when glucocorticoids are withdrawn, has not been confirmed. Previous randomized, controlled studies of AZA for remission maintenance enrolled only patients with newly diagnosed disease (5,10) or maintained low-dose glucocorticoids for at least 18–24 months (5,10,21). A recent retrospective series demonstrated that longer duration of AZA or MTX therapy reduced the rate of relapse (7). However, that study examined only newly diagnosed patients whose disease had remained in remission for at least 18 months (7). Thus, previous trials have not addressed the specific patient subgroup described in the present study. In addition, the MAINRITSAN study demonstrated that despite concomitant glucocorticoid therapy for at least 18 months, 29% of patients treated with AZA experienced a severe relapse within 28 months, further calling into question the efficacy of AZA for maintaining disease remission (21).

The use of low-dose glucocorticoids for remission maintenance remains a subject of controversy (22,23). It is notable that the median prednisone dosage among patients in this study who had a second disease relapse while receiving glucocorticoids was 7.5 mg/day. These data support the concept that many disease relapses occur in AAV despite continuous prednisone doses higher than those regarded generally as "low dose." Although the followup period in this study was likely too short to detect differences in treatment-related adverse events or damage, a recent study in patients with rheumatoid arthritis demonstrated that treatment with $\geq$8 mg/day prednisone was associated with an increase in death from any cause in a dose-dependent manner, suggesting that there may be substantial long-term effects of prolonged glucocorticoid use in doses required to maintain disease stability in GPA (24). The currently ongoing "The Assessment of Prednisone In Remission" study may add to our understanding of the utility of low-dose prednisone in maintaining disease remission in AAV (25).

Our study has several limitations. The starting prednisone dose for the treatment of nonsevere relapses was not standardized. However, the protocol permitted the investigator to select the appropriate starting dose based on clinical judgment, which accurately reflects the approach used in clinical practice. Moreover, the starting dose did not appear to affect the likelihood of achieving remission or experiencing a second relapse. The majority of patients in this study were PR3-ANCA positive, a population that is known to be at higher risk of relapse (9,10,26–28). Therefore, the generalizability of our findings to MPO-ANCA–positive patients is not certain. Our study also has several strengths, including the protocolized study design, collection of data within the confines of a label-enabling clinical trial with rigorous data monitoring and regulatory agency oversight, and close patient followup throughout the study.

In conclusion, treatment of nonsevere relapses in AAV with a temporary increase in the glucocorticoid dose restores disease remission in most patients, but recurrent relapses within a relatively short time period remain common. Alternative approaches to the treatment of nonsevere relapses must be considered, including continuing glucocorticoids indefinitely or the use of B cell depletion in some patients.

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.

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Analysis and interpretation of data. Miloslavsky, Specks, Merkel, Seo, Spiera, Langford, Hoffman, Kallenberg, St.Clair, Tchao, Ding, Iklé, Villareal, Lim, Fervenza, Stone.

ROLE OF THE STUDY SPONSOR

Genentech and Biogen Idec had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Genentech and Biogen Idec.

ADDITIONAL DISCLOSURE

Authors Iklé and Villareal are employees of Rho, a contract research organization.

REFERENCES

1. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. N Engl J Med 1979;301:235–8.
2. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351–61.
3. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al, for the RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
4. De Groot K, Muhler M, Reinhold-Keller E, Paulsen J, Gross WL. Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol 1998;25:492–5.
5. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al, for the European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381–8.
6. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al, for the European Vasculitis Study Group. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheum 2005;52:2461–9.
7. Springer J, Nutter B, Langford CA, Hoffman GS, Villa-Forte A. Granulomatosis with polyangiitis (Wegener's): impact of maintenance therapy duration. Medicine (Baltimore) 2014;93:82–90.
8. De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al, EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.
9. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al, for the European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.
10. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al, for the French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790–803.
11. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al, for the European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.
12. Carrington CB, Liebow AA. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 1966;41:497–527.
13. Jayne D. Update on the European Vasculitis Study Group trials. Curr Opin Rheumatol 2001;13:48–55.
14. Specks U, Merkel PA, Hoffman GS, Langford CA, Spiera R, Seo P, et al, for the RAVE-ITN Research Group. Design of the Rituximab in ANCA-associated Vasculitis (RAVE) trial. Open Arthritis J 2011;4:1–18.
15. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al, for the International Network for the Study of the Systemic Vasculitides (INSSYS). A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. Arthritis Rheum 2001;44:912–20.
16. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al, for the RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.
17. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371–80.
18. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. Arthritis Rheum 1992;35:1322–9.
19. Langford CA, Talar-Williams C, Sneller MC. Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis: long-term renal outcome in patients with glomerulonephritis. Arthritis Rheum 2000;43:1836–40.
20. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al, for the Rituximab in ANCA-Associated Vasculitis–Immune Tolerance Network Research Group. Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheumatol 2014;66:3151–9.
21. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al, for the French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
22. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol 2012;7:240–7.
23. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody–associated vasculitis: a meta-analysis. Arthritis Care Res (Hoboken) 2010;62:1166–73.
24. Del Rincon I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol 2014;66:264–72.
25. National Library of Medicine: National Institutes of health. ClinicalTrials.gov study record: The Assessment of Prednisone In Remission Trial (TAPIR): patient centric approach. URL: https://clinicaltrials.gov/ct2/show/NCT01933724.
26. Franssen C, Gans R, Kallenberg C, Hageluken C, Hoorntje S. Disease spectrum of patients with antineutrophil cytoplasmic autoantibodies of defined specificity: distinct differences between patients with anti-proteinase 3 and anti-myeloperoxidase autoantibodies. J Intern Med 1998;244:209–16.
27. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis 2012;71:955–60.
28. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al, on behalf of the European Vasculitis Study Group. Risk factors for relapse of antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheum 2012;64:542–8.