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Clinical Outcomes of Treatment of Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Based on ANCA Type

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Abstract

Objective—To evaluate whether the classification of ANCA-associated vasculitis (AAV) patients according to ANCA type (anti-proteinase 3 [PR3] or anti-myeloperoxidase [MPO] antibodies) predicts treatment response.

Methods—Treatment responses were assessed among patients enrolled in the Rituximab in ANCA-associated Vasculitis trial according to both AAV diagnosis (granulomatosis with polyangiitis [GPA]/microscopic polyangiitis [MPA]) and ANCA type (PR3-AAV/MPO-AAV). Complete remission (CR) was defined as disease activity score of 0 and successful completion of the prednisone taper.

Results—PR3-AAV patients treated with rituximab (RTX) achieved CR at 6 months more frequently than did those randomized to cyclophosphamide (CYC)/azathioprine (AZA) (65% versus 48%; P=0.04). The odds ratio (OR) for CR at 6 months among PR3-AAV patients treated with RTX as opposed to CYC/AZA was 2.11 (95%CI 1.04–4.30) in analyses adjusted for age, sex, and new-onset versus relapsing disease at baseline. PR3-AAV patients with relapsing disease achieved CR more often following RTX treatment at 6 months (OR3.57; 95%CI 1.43–8.93); 12 months (OR4.32; 95%CI 1.53–12.15); and 18 months (OR3.06; 95%CI 1.05–8.97). No

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association between treatment and CR was observed in the MPO-AAV patient subset or in groups divided according to AAV diagnosis.

Conclusion—PR3-AAV patients respond better to RTX than to CYC/AZA. An ANCA type-based classification may guide immunosuppression in AAV.

Keywords

ANCA; granulomatosis with polyangiitis; microscopic polyangiitis; rituximab; cyclophosphamide

INTRODUCTION

Rituximab (RTX) and cyclophosphamide (CYC) are considered standard of care alternatives for induction of remission in patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [1–4]. A subgroup analysis of the Rituximab in AAV trial (RAVE) demonstrated that RTX was superior to CYC in subjects with relapsing disease. However, no other subset of patients has been recognized to derive clear benefit from one specific immunosuppressive strategy as opposed to the other [1–3, 5–7]. The identification of biomarkers that improve the individualization of treatment decisions would represent an important contribution to the care of patients with AAV.

We evaluated two different classification systems for AAV in a well-characterized group of patients: one based on the patient's specific AAV diagnosis (GPA versus MPA), and the other on the patient's specific ANCA type (PR3-AAV versus MPO-AAV). The objective of this study was to determine if the classification of AAV patients solely based on their ANCA type predicts treatment response and other clinical outcomes.

METHODS

Patient Groups and Treatment Regimens

The RAVE study was a double-blind, placebo-controlled trial that randomized 197 patients to receive either RTX (375 mg/m^2 intravenously weekly for 4 weeks; RTX group, n=99) or CYC (2 mg/kg for 3–6 months) followed by maintenance azathioprine (AZA; 2 mg/kg, up to 150 mg/d [CYC/AZA group, n=98]). Both groups received a 5.5-month prednisone taper and were followed for 18 months. Details of the trial design and the main study results have been published [2, 5, 8].

Definition of Predictor and Outcome Variables

We classified patients by their specific AAV diagnoses (GPA or MPA), rendered during the conduct of the trial. These diagnoses were based upon the 1994 Chapel Hill Consensus on vasculitis nomenclature [9]. We also classified patients according to whether they were PR3- or MPO-ANCA positive. We refer to the subsets generated by the classification as PR3-AAV and MPO-AAV, respectively. Within each classification system, we compared patients' demographics, baseline clinical manifestations, and response to treatment stratified by treatment assignment (RTX versus CYC/AZA). In addition, we analyzed the number and severity of disease flares, time to flare, cumulative glucocorticoid use, disease damage, and the percentage of patients who became ANCA-negative at 6 months.

Vasculitis activity was measured using the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG)[10]. Patients with BVAS/WG ≥1 were considered to have active disease. Complete remission (CR) as defined as a BVAS/WG of 0 and successful prednisone taper completion. Severe flares were defined as a BVAS/WG ≥3. Flares not meeting criteria for severe were classified as non-severe. Damage was graded according to the Vasculitis Damage Index (VDI) [11]

Statistical Analysis

Continuous and categorical variables were compared between pairs of groups (GPA versus MPA and PR3-AAV versus MPO-AAV) using the Wilcoxon Rank-Sum test and the Chi-square, and Fisher's exact tests, respectively. Multivariable logistic regression was utilized to account for potential confounders in the analysis of selected dichotomous outcomes. Results were expressed as odds ratios (OR) and 95% confidence intervals (CI).

To determine the effect of RTX versus CYC/AZA on the outcome of CR at 6, 12, and 18 months, we created logistic regression models within each classification category (GPA, MPA, PR3-AAV, and MPO-AAV). The models included age, sex, and the status of newly-diagnosed versus relapsing disease at baseline as covariates. For each classification category, we completed subgroup analyses limited to patients with newly-diagnosed and relapsed disease at baseline. VDI scores were compared over time between pairs of groups (GPA versus MPA, PR3-AAV versus MPO-AAV) using repeated measures mixed-effect models. The cut-off for statistical significance was 0.05; all P-values were two-sided. SAS 9.2 and R 3.0.0 were used for the statistical analyses.

RESULTS

The RAVE trial enrolled 197 patients. When divided by AAV diagnosis, 148 patients were classified as GPA (86% anti-PR3 positive) and 48 as MPA (92% anti-MPO positive) (Table 1). One subject could not be categorized clearly as either GPA or MPA. When divided by ANCA type, 131 patients were classified as PR3-AAV (97% GPA) and 66 as MPO-AAV (70% MPA) (Table 1). Twenty patients with GPA (14%) had anti-MPO antibodies and 4 with MPA (8%) had anti-PR3 antibodies.

Demographics and Baseline Disease Characteristics

Considerable overlap existed between both classification systems in terms of demographic data and baseline clinical manifestations (Table 1 and online Supplementary Text). Patients classified as GPA and PR3-AAV were more likely to have relapsing disease at baseline compared to those classified as MPA and MPO-AAV, respectively. The mean BVAS/WG at study onset was equivalent across all subsets.

Response to Treatment

CR at 6 months was achieved in 115 subjects (RTX n=63; CYC/AZA n=52). Patients with PR3-AAV met this outcome significantly more often when treated with RTX as opposed to CYC/AZA (65% versus 48%; P=0.04) (Table 2). Multivariate analysis adjusting for differences in age, sex, and the status of new-onset versus relapsing disease at baseline

yielded an OR for CR at 6 months of 2.11 (95%CI 1.04 to 4.30; P=0.04), favoring RTX over CYC/AZA (Table 3). In this model, the OR for CR at 6 months associated with the status of newly-diagnosed versus relapsing disease was 1.74 (95%CI 0.83 to 3.66; P=0.14). In contrast, the proportion of MPO-AAV patients in CR at 6 months did not differ according to induction regimen (RTX 61% and CYC/AZA 64%; P=0.80) (Table 2). The non-differential response to treatment among patients with MPO-AAV persisted in multivariate-adjusted analyses (data not shown).

The percentage of patients achieving CR at 6 months was equivalent between treatment arms for both patients with GPA (RTX 63% and CYC/AZA 50%; P=0.11) and those with MPA (67% RTX and 63% CYC/AZA; P=0.76) (Table 2). Neither treatment was favored among patients with GPA or MPA in multivariate-adjusted analyses (data not shown).

Eighty-one patients (62%) with PR3-AAV had relapsing disease at baseline. Of those, 42 received RTX and 39 received CYC/AZA. Univariate analyses showed that CR at 6, 12, and 18 months was achieved significantly more often in patients assigned to RTX: 6-months, RTX 67% versus CYC/AZA 36% (P<0.01); 12-months, RTX 48% versus CYC/AZA 18% (P<0.01); and 18-months, RTX 36% versus CYC/AZA 15% (P=0.04). Multivariate analyses demonstrated that the better response to RTX in this subgroup persisted following adjustments for differences in age and sex (Table 3). The ORs (95%CI) for attaining CR at 6, 12, and 18 months were 3.57 (1.43 to 8.93; P<0.01); 4.32 (1.53 to 12.15; P<0.01); and 3.06 (1.05 to 8.97; P=0.04), respectively.

When divided by AAV diagnosis, 91 patients (61%) classified as GPA had relapsing disease at baseline. Of those, 47 received RTX and 44 received CYC/AZA. Univariate analyses showed that CR was achieved significantly more often among patients assigned to RTX at 6 months (RTX 66% versus CYC/AZA 39% [P<0.01]) and 12 months (RTX 47% versus CYC/AZA 23% [P=0.01]), but not at 18 months (RTX 38% versus CYC/AZA 21% [P=0.06]). In multivariate analyses, the ORs (95%CI) comparing RTX to CYC/AZA for CR at 6, 12, and 18 months among GPA patients with relapsing disease at baseline were 3.11 (1.32 to 7.35; P=0.01), 3.11 (1.23 to 7.86; P=0.02), and 2.48 (0.96 to 6.39; P=0.06), respectively.

Univariate and multivariate analysis of CR at 6, 12, and 18 months demonstrated equivalent response to RTX and CYC/AZA treatment in all other subgroups studied (i.e., newly-diagnosed PR3-AAV, newly-diagnosed MPO-AAV, relapsed MPO-AAV, newly-diagnosed GPA, newly-diagnosed MPA and relapsed MPA) (data not shown).

Other Outcomes

In general, there were no significant differences between both classification systems in regards to disease relapse, damage, and cumulative glucocorticoid use (online Supplementary Text, Supplementary Table 1, and Supplementary Table 2). Unlike MPO-AAV patients, PR3-AAV patients became ANCA-negative at 6 months significantly more often when treated with RTX as opposed to CYC/AZA (online Supplementary Text).

DISCUSSION

Analysis of these prospective clinical trial data demonstrate that patients with PR3-AAV were more than twice as likely to achieve CR at 6 months if treated with RTX rather than with CYC/AZA. In addition, among patients with PR3-AAV who had relapsing disease at baseline, the risk of disease flare in RTX-treated patients was lower not only at 6 months, but also at 12 and 18 months, despite the fact that patients randomized to RTX were not re-treated pre-emptively with a maintenance regimen.

Prior analyses of the RAVE cohort identified the history of disease relapse as a predictor of better response to RTX over CYC. However, AAV relapses tend to occur months after diagnosis and therapy initiation. In addition, both disease relapse and the burden of prior immunosuppression are factors associated with adverse events including infection, disease damage, and mortality [12–14]. Therefore, previous disease relapse is suboptimal as a biomarker to guide treatment decisions. A readily available objective measure such as ANCA testing overcomes the limitation of having to wait until patients declare themselves as relapsers, offering clinicians the opportunity to make rational treatment decisions early during the course of the disease. Additional studies are required to determine if the institution of this approach leads to better long-term outcomes in AAV.

Our results not only have implications for remission-induction, but also for remission-maintenance. Following remission-induction with CYC, RTX dosing at fixed intervals has been shown in one study to be superior to AZA for prevention of disease relapses [3]. However, the risk: benefit ratio of pre-emptive B-cell depletion for different patient subpopulations is currently uncertain. Therefore, knowing that patients with PR3-AAV constitute a subgroup with a high risk of relapse but a higher likelihood of response to RTX should inform both current clinical practice and the design of future clinical trials [15–17].

Our study has potential limitations. First, although still generalizable to the majority of patients with AAV [18–20], extrapolation of our findings to ANCA-negative patients is not possible. Second, our data derive from a *post hoc* clinical trial analysis and therefore should be confirmed in additional prospective studies. Finally, the relatively small sample size might have led to low statistical power to detect treatment differences in other subgroups. Larger studies, especially of MPO-AAV patients, are needed.

In conclusion, our analysis reinforces and expands the notion that an ANCA-based classification provides valuable predictive information in AAV. Patients with PR3-AAV are more likely to achieve and maintain CR if treated with RTX as opposed to CYC/AZA. This observation may directly influence the choice of remission induction therapy for this AAV subset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of patients with AAV according to serological and clinicopathological classifications[1]

	PR3-AAV (n = 131)	MPO-AAV (n = 66)	P-value	GPA (n = 148)	MPA (n= 48)	P-value
Age at diagnosis, mean (SD)	46 (15)	58 (16)	<0.01	46 (15)	60 (16)	<0.01
Male sex, number (%)	76 (58)	24 (36)	<0.01	80 (54)	18 (38)	0.04
Relapsed disease, number (%)	81 (62)	20 (30)	<0.01	91 (62)	9 (19)	<0.01
Baseline BVAS/WG score, mean (SD)	8 (3.2)	8.1 (3.1)	0.87	8.2 (3.3)	7.3 (2.3)	0.09
Number of major items, mean (SD)	1.4 (1.0)	1.9 (0.9)	<0.01	1.5 (1.0)	1.9 (0.8)	<0.01
Number of minor items, mean (SD)	3.7 (2.2)	2.4 (2.0)	<0.01	3.8 (2.1)	1.7 (1.6)	<0.01
Organs involved, number (%)						
Constitutional	93 (71)	35 (53)	0.01	105 (71)	21 (44)	<0.01
Cutaneous	34 (26)	13 (20)	0.33	38 (26)	8 (17)	0.19
Mucous membranes and eyes	42 (32)	9 (14)	<0.01	46 (31)	5 (10)	<0.01
Ear, nose and throat (ENT)	92 (70)	22 (33)	<0.01	106 (72)	8 (17)	<0.01
Cardiovascular	2 (1.5)	2 (3)	0.60	3 (2)	1 (2)	>0.99
Gastrointestinal	2 (1.5)	1 (1.5)	>0.99	2 (1.5)	1 (2)	0.57
Pulmonary	74 (57)	30 (46)	0.14	83 (57)	20 (42)	0.08
Alveolar haemorrhage	31 (24)	13 (20)	0.53	33 (22)	11 (23)	0.95
Parenchymal nodules or cavities	36 (28)	8 (12)	0.02	42 (29)	1 (2)	<0.01
Renal	77 (59)	52 (79)	<0.01	89 (61)	40 (83)	<0.01
Serum creatinine, mean (SD)	1.32 (0.7)	1.69 (0.8)	<0.01	1.33 (0.7)	1.8 (0.9)	<0.01
Neurologic	21 (16)	18 (27)	0.06	28 (19)	9 (19)	0.96
Peripheral neuropathy	20 (15)	18 (27)	0.04	27 (18)	9 (19)	0.95

[1]One patient had an indeterminate type of AAV.

AAV = ANCA-associated vasculitis; GPA = granulomatous polyangiitis; MPA = microscopic polyangiitis; SD = standard deviation; BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis

Table 2

Treatment outcomes in patients with AAV according to serological and clinicopathological classifications[1, 2]

	PR3-AAV			MPO-AAV			GPA			MPA		
	RTX (n=66)	**CYC/AZA (n=65)**	**P**	**RTX (n=33)**	**CYC/AZA (n=33)**	**P**	**RTX (n=74)**	**CYC/AZA (n=74)**	**P**	**RTX (n=24)**	**CYC/AZA (n=24)**	**P**
CR at 6 months	43 (65)	31(48)	0.04	20 (61)	21 (64)	0.80	46 (63)	37 (50)	0.11	16 (67)	15 (63)	0.76
CR at 12 months	31 (47)	21 (32)	0.09	16 (49)	17 (52)	0.81	33 (45)	27 (37)	0.28	14 (58)	11 (46)	0.39
CR at 18 months	24 (36)	19 (29)	0.39	15 (46)	13 (39)	0.62	27 (37)	23 (31)	0.45	12 (50)	9 (38)	0.38

[1] Values represent number of patients and percentages (%).

[2] One patient had an indeterminate type of AAV.

AAV = ANCA-associated vasculitis; GPA = granulomatous polyangiitis; MPA = microscopic polyangiitis; RTX = rituximab; CYC = cyclophosphamide; AZA = azathioprine; CR = complete remission; SD = standard deviation

Table 3

Treatment response among patients with PR3-AAV who received RTX vs. patients with PR3-AAV who received CYC/AZA

	OR[1]	95% CI	P-value
All patients with PR3-AAV (n = 131) [2]			
CR at 6 months	2.11	1.04 – 4.30	0.04
CR at 12 months	1.96	0.95 – 4.05	0.07
CR at 18 months	1.44	0.68 – 3.05	0.34
Patients with PR3-AAV with relapsing disease at baseline (n = 81)[3]			
CR at 6 months	3.57	1.43 – 8.93	<0.01
CR at 12 months	4.32	1.53 – 12.15	<0.01
CR at 18 months	3.06	1.05 – 8.97	0.04

[1]Comparison of RTX group versus CYC/AZA group.

[2]Covariates included in the model: treatment (RTX or CYC/AZA), age, sex, and status of relapsing versus new onset disease at baseline.

[3]Covariates included in the model: treatment (RTX or CYC/AZA), age, and sex.

RTX = rituximab; CYC = cyclophosphamide; AZA = azathioprine; AAV = ANCA associated vasculitis; CR = complete remission; OR = odds ratio; CI = confidence interval