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Myeloperoxidase–Antineutrophil Cytoplasmic Antibody (ANCA)–Positive and ANCA-Negative Patients With Granulomatosis With Polyangiitis (Wegener's)

Distinct Patient Subsets

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Objective. **To examine the relationship of antineutrophil cytoplasmic antibody (ANCA) type and ANCA-associated vasculitis (AAV) diagnosis with demographic features, disease manifestations, and clinical outcomes. We focused on patients who account for the differences between ANCA type and disease type classifications: antimyeloperoxidase (MPO)–ANCA–positive and ANCA-negative patients with granulomatosis with polyangiitis (Wegener's) (GPA).**

Methods. **We performed a pooled analysis of the Wegener's Granulomatosis Etanercept Trial and the Rituximab in ANCA-Associated Vasculitis trial comparing patients with MPO-ANCA–positive GPA and patients with ANCA-negative GPA to patients with proteinase 3 (PR3)–ANCA–positive GPA and patients with MPO-ANCA–positive microscopic polyangiitis (MPA).**

Results. **Of the 365 patients analyzed, 273 (75%) had PR3-ANCA–positive GPA, 33 (9%) had MPO-ANCA–positive GPA, 15 (4%) had ANCA-negative GPA, and 44 (12%) had MPO-ANCA–positive MPA. MPO-ANCA–positive GPA patients were younger at diagnosis compared to MPO-ANCA–positive MPA patients (53 versus 61 years; $P = 0.02$). Their disease manifestations and rates of relapse were similar to those of PR3-ANCA–positive GPA patients. Relapse was more frequent in MPO-ANCA–positive GPA patients than in patients with MPO-ANCA–positive MPA at trial entry as well as at 12 and 18 months. ANCA-negative patients with GPA had lower Birmingham Vasculitis Activity Score for Wegener's Granulomatosis scores at trial entry than PR3-ANCA–positive patients with GPA (4.5 versus 7.7; $P < 0.01$), primarily because of a lower prevalence of renal involvement.**

Conclusion. **We were unable to demonstrate important clinical differences between MPO-ANCA–positive and PR3-ANCA–positive patients with GPA.**

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The risk of relapse was associated more closely with disease type than with ANCA type in this patient cohort. These findings deserve consideration in the assessment of relapse risk in patients with AAV.

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are a group of disorders associated with inflammation of small and medium-sized vessels. Identifying subgroups of patients within AAV is important for determining prognosis, anticipating patterns of organ involvement, predicting treatment response, and stratifying patients with regard to relapse risk. To date, patients with AAV enrolled in clinical trials have been categorized into those with granulomatosis with polyangiitis (Wegener's) (GPA) and those with microscopic polyangiitis (MPA). Most patients with GPA and MPA are ANCA positive, with an antigen specificity for either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA).

Recently, several clinical and genome-wide association studies (GWAS) have suggested that classification based on ANCA type, i.e., PR3-ANCA positivity as opposed to MPO-ANCA positivity, may be more relevant clinically than the traditional classification based on specific AAV diagnosis, i.e., GPA versus MPA (1–3). A GWAS by Lyons and colleagues demonstrated that genetic associations cluster more closely with ANCA type as compared to disease type (1). Studies by Mahr et al (2) and Lionaki et al (3) showed that ANCA type is a better predictor of clinical outcomes such as death and relapse than is disease type, with PR3-ANCA presence being predictive of a higher risk of relapse and lower risk of death than disease type categorization.

Most patients with clinical diagnoses of GPA are PR3-ANCA positive, but a significant minority are MPO-ANCA positive or are negative for ANCA (4,5). The differences between classifications based on the specific AAV diagnosis as opposed to ANCA type are driven primarily by GPA patients who are MPO-ANCA positive or ANCA negative. However, little scrutiny has been given to these GPA subsets (6–9). Based on the recent studies comparing disease type and ANCA type classifications, we hypothesized that ANCA type would be predictive of clinical manifestations and risk of relapse within the same disease subset (e.g., GPA). We therefore analyzed the clinical features and treatment outcomes of MPO-ANCA–positive GPA and ANCA-negative GPA patients enrolled in the Wegener's Granulomatosis Etanercept Trial (WGET) (10) or the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (11). We then compared these subgroups of patients to those with traditionally "concordant" ANCA and disease types: MPO-ANCA–positive GPA patients versus PR3-ANCA–positive GPA patients; MPO-ANCA–positive GPA patients versus MPO-ANCA–positive MPA patients; and ANCA-negative GPA patients versus PR3-ANCA–positive GPA patients.

PATIENTS AND METHODS

Patients and treatments. We analyzed patients from both the WGET and RAVE trials in order to obtain a larger sample size of MPO-ANCA–positive patients. The ANCA-negative GPA patients were obtained from the WGET only, because ANCA positivity was an inclusion criterion for RAVE. Details of the WGET and RAVE designs have been published previously (11,12).

Briefly, WGET was a randomized, double-blind, placebo-controlled trial that enrolled patients with GPA, as defined by the American College of Rheumatology classification criteria (13). Patients classified as having GPA met at least 2 of the following 4 criteria: nasal/oral inflammation, chest radiographic abnormalities, active urinary sediment, and granulomatous inflammation on biopsy. ANCA positivity was not required for enrollment. WGET participants were assigned to receive etanercept (25 mg twice weekly) or placebo, in addition to therapy with daily cyclophosphamide (CYC; 2 mg/kg, adjusted for renal insufficiency) for those with severe disease and methotrexate (MTX; up to 25 mg/week) for those with nonsevere ("limited") disease (14). Patients in the etanercept and comparison groups received the same glucocorticoid treatment regimen, which called for the discontinuation of prednisone by 6 months. After remission was achieved, patients were treated with MTX, and those with renal insufficiency were treated with azathioprine (AZA; 2 mg/kg) for 12 months, followed by a taper.

RAVE was a randomized, double-blind, double-dummy, placebo-controlled trial that enrolled patients with severe GPA or MPA. All patients were ANCA positive (12). GPA and MPA were defined by the Chapel Hill Consensus Conference (CHCC) nomenclature (15). The CHCC definition of GPA stipulated that the use of this diagnostic label be restricted to patients with granulomatous inflammation demonstrated by histopathology or clinical and radiographic findings generally consistent with that histopathologic finding (e.g., pulmonary nodules or sinusitis). Patients were assigned 1:1 to receive either: 1) daily 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; or 2) rituximab (375 mg/m^2 once weekly for 4 weeks) followed by AZA placebo. The glucocorticoid taper in RAVE called for discontinuation of prednisone within 6 months.

ANCA measurements. ANCA type and titer were determined by standard indirect immunofluorescence and antigen-specific immunoassays as described previously for the WGET and RAVE trial cohorts (5,11). In both trials, all ANCA measurements were performed simultaneously on the same enzyme-linked immunosorbent assay (ELISA) plate at a single laboratory (Mayo Clinic). Patients who were positive for both MPO-ANCA and PR3-ANCA (n = 4) were excluded from the analysis. All patients who had a cytoplasmic ANCA pattern detected by immunofluorescence were PR3-ANCA positive. Two patients in the WGET had a perinuclear ANCA (pANCA) staining pattern but were negative for PR3- and MPO-ANCAs. One of these 2 patients tested positive for antibodies directed against human neutrophil elastase (16) and was excluded from the analysis. The other patient was included in

the ANCA-negative group. No patients changed from one ANCA type to the other during the course of the trials.

Assessments. Disease activity in both trials was assessed by the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) (17). Disease damage was assessed by the Vasculitis Damage Index (VDI) (18). The WGET assessed patients at 6 and 12 weeks, and then every 3 months. Patients in the RAVE trial were assessed at 1, 2, 4, and 6 months and every 3 months thereafter. Patient data were analyzed through the 18-month time point.

Disease manifestations and clinical outcomes. Disease manifestations were assessed at trial entry and at each study visit. For the purposes of comparing clinical manifestations between subgroups of patients, we examined the clinical manifestations recorded throughout both trials, counting each manifestation only once, regardless of whether it occurred at trial entry or during relapse.

We examined the clinical manifestations within 2 broad categories: 1) those associated with GPA (19), including upper and lower airway disease (sino-nasal manifestations, conductive hearing loss, subglottic stenosis, and endobronchial lesions), ocular disease (scleritis and orbital mass), and pulmonary nodules (4); and 2) capillaritis-related features (purpura, glomerulonephritis, pulmonary hemorrhage, and vasculitic neuropathy) (19).

We analyzed the rates of disease relapse as the primary clinical outcome. Relapses were defined in both trials as an increase in the BVAS/WG of $\geq$1 point. Severe relapses were defined as an increase in the BVAS/WG of $>$3 points or 1 new major BVAS/WG item. Relapses not meeting criteria for severe relapse were classified as nonsevere (12,14,20).

Statistical analysis. Binary outcomes were compared using the chi-square or Fisher's exact test, depending on the cell sizes. Continuous outcomes between groups were compared using Student's *t*-test. All statistical tests were 2-sided, and *P* values less than 0.05 were considered significant. SAS version 9.1 was used for all statistical analyses.

RESULTS

The WGET and RAVE trials included a total of 377 patients. We excluded 12 patients from the analysis. Five of the excluded patients had diagnoses of MPA but were PR3-ANCA positive. While this subgroup was too small to fully analyze, all 5 patients had alveolar hemorrhage, 2 had nephritis, 1 had purpura, and 1 had scleritis. Of the 7 other excluded patients, 4 were positive for both MPO and PR3-ANCA, 1 had an indeterminate disease type, 1 had an unknown ANCA status, and 1 tested positive for antibodies directed against human neutrophil elastase. Among the 365 remaining patients, 321 (88%) had GPA and 44 (12%) had MPA. All of the MPA patients analyzed had MPO-ANCA and were subjects in the RAVE trial. Of the patients with GPA, 273 (85%) had PR3-ANCA, 33 (10%) had MPO-ANCA, and 15 (5%) were ANCA negative.

MPO-ANCA–positive GPA patients versus PR3-ANCA–positive GPA patients. MPO-ANCA–positive patients with GPA were more likely to be female compared to their PR3-ANCA–positive GPA counterparts (58% versus 39%; $P = 0.04$) (Table 1), but were of similar age. The mean BVAS/WG at study entry for the MPO-ANCA–positive patients with GPA was similar to that of PR3-ANCA–positive patients with GPA (8.2 versus 7.7; $P = 0.36$).

Disease manifestations typically associated with GPA did not differ significantly between the 2 groups,

Table 1. Clinical characteristics and relapse rates of PR3-ANCA–positive patients with GPA and MPO-ANCA–positive patients with GPA*

	MPO-ANCA–positive GPA (n = 33)	PR3-ANCA–positive GPA (n = 273)
Age, mean	53	50
% male	42	61†
BVAS/WG, mean	8.2	7.7
VDI, mean	0.9	1.3
Clinical characteristic		
Granulomatous features on histology, no./no. assessed (%)	14/30 (47)	95/209 (45)
Ear/nose/throat	25 (76)	217 (79)
Bloody nasal discharge	18 (55)	184 (67)
Sinus involvement	13 (39)	133 (49)
Subglottic inflammation	3 (9)	31 (11)
Hearing loss, conductive	3 (9)	61 (22)
Mucous membranes/eyes	9 (27)	94 (34)
Conjunctivitis/episcleritis	5 (15)	56 (21)
Uveitis	0 (0)	3 (1)
Scleritis	0 (0)	22 (8)
Orbital mass/proptosis	2 (6)	11 (4)
Heart	0 (0)	4 (2)
Gastrointestinal tract	0 (0)	4 (2)
Pulmonary	20 (61)	170 (62)
Endobronchial involvement	0 (0)	28 (10)
Nodules or cavities	11 (33)	92 (34)
Alveolar hemorrhage	7 (21)	65 (24)
Cutaneous	8 (24)	66 (24)
Renal	22 (67)	170 (62)
GFR (MDRD), mean	56.9	66.7
Nervous system	9 (27)	44 (16)
Sensory peripheral neuropathy	6 (18)	36 (13)
Motor mononeuritis	3 (9)	12 (4)
Relapse rate		
Relapsing disease at trial entry	19 (58)	156 (57)
Participants with relapse at 6 months	8 (24)	71 (26)
Severe relapse	1 (3)	23 (9)
Participants with relapse at 12 months	12 (36)	127 (47)
Severe relapse	5 (15)	44 (16)
Participants with relapse at 18 months	15 (45)	148 (54)
Severe relapse	7 (21)	63 (23)

* Except where indicated otherwise, values are the number (%). PR3-ANCA = proteinase 3–antineutrophil cytoplasmic antibody; GPA = granulomatosis with polyangiitis (Wegener's); BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; VDI = Vasculitis Damage Index; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

† $P = 0.04$ versus patients with myeloperoxidase-ANCA (MPO-ANCA)–positive GPA.

Table 2. Clinical characteristics and relapse rates of MPO-ANCA–positive patients with GPA and MPO-ANCA–positive patients with MPA*

	MPO-ANCA–positive GPA (n = 33)	MPO-ANCA–positive MPA (n = 44)	*P*
Age, mean	53	61	0.02
% male	42	36	0.59
BVAS/WG, mean	8.2	7.2	0.16
VDI, mean	0.9	0.9	0.96
Clinical characteristic			
Granulomatous features on histology, no./no. assessed (%)	14/30 (47)	0/33 (0)	<0.01
Ear/nose/throat	25 (76)	8 (18)	<0.01
Bloody nasal discharge	18 (55)	7 (16)	<0.01
Sinus involvement	13 (39)	1 (2)	<0.01
Subglottic inflammation	3 (9)	0 (0)	0.07
Hearing loss, conductive	3 (9)	0 (0)	0.07
Mucous membranes/eyes	9 (27)	6 (14)	0.13
Conjunctivitis/episcleritis	5 (15)	3 (7)	0.66
Uveitis	0 (0)	0 (0)	–
Scleritis	0 (0)	1 (2)	>0.99
Orbital mass/proptosis	2 (6)	0 (0)	0.18
Heart	0 (0)	0 (0)	–
Gastrointestinal tract	0 (0)	1 (2)	>0.99
Pulmonary	20 (61)	18 (41)	0.09
Endobronchial involvement	0 (0)	0 (0)	0.36
Nodules or cavities	11 (33)	1 (2)	<0.01
Alveolar hemorrhage	7 (21)	8 (18)	0.74
Cutaneous	8 (24)	7 (16)	0.36
Renal	22 (67)	38 (86)	0.04
GFR (MDRD), mean	56.9	47.9	0.23
Nervous system	9 (27)	9 (20)	0.48
Sensory peripheral neuropathy	6 (18)	9 (20)	0.80
Motor mononeuritis	3 (9)	6 (14)	0.54
Relapse rate			
Relapsing disease at trial entry	19 (58)	8 (18)	<0.01
Participants with relapse at 6 months	8 (24)	4 (9)	0.07
Severe relapse	1 (3)	2 (5)	>0.99
Participants with relapse at 12 months	12 (36)	5 (11)	<0.01
Severe relapse	5 (15)	3 (7)	0.28
Participants with relapse at 18 months	15 (45)	8 (18)	<0.01
Severe relapse	7 (21)	5 (11)	0.24

* Except where indicated otherwise, values are the number (%). MPA = microscopic polyangiitis (see Table 1 for other definitions).

including sino-nasal involvement, subglottic inflammation, conductive hearing loss, frequency of orbital masses, and pulmonary nodules. Of the 239 patients for whom histologic data were recorded (78%), granulomatous inflammation was detected on biopsy in a similar percentage of patients in both groups (45% PR3-ANCA–positive GPA versus 47% MPO-ANCA–positive GPA; $P = 0.90$). With regard to "capillaritis-related" features, alveolar hemorrhage, glomerulonephritis, and peripheral neuropathy occurred with equal frequency and severity in both groups.

The percentages of patients with 1 or more relapses as opposed to newly diagnosed disease at trial entry were equivalent in the 2 groups: 57% PR3-ANCA–positive GPA versus 58% MPO-ANCA–positive GPA ($P = 0.96$). There were no differences in rates of relapse during the course of follow-up (54% PR3-ANCA–positive GPA versus 45% MPO-ANCA–positive GPA; $P = 0.34$). Disease damage, as measured by the VDI, did not differ between groups over the course of the follow-up period.

MPO-ANCA–positive GPA patients versus MPO-ANCA–positive MPA patients. MPO-ANCA–positive patients with GPA were significantly younger than MPO-ANCA–positive patients with MPA (mean age 53 versus 61 years; $P = 0.02$) (Table 2), but the sex distributions between the 2 groups were equivalent. Features associated with GPA, such as bloody nasal discharge (55% versus 16%; $P < 0.01$), sinus involvement (39% versus 2%; $P < 0.01$), and lung nodules or cavities (33% versus 2%; $P < 0.01$) were more common among the

Table 3. Clinical characteristics and relapse rates of ANCA-negative patients with GPA and PR3-ANCA–positive patients with GPA*

	ANCA-negative GPA (n = 15)	PR3-ANCA–positive GPA (n = 273)	*P*
Age, mean	50	50	0.81
% male	33	61	0.03
BVAS/WG, mean	4.5	7.7	<0.01
VDI, mean	2.0	1.3	0.08
Clinical characteristic			
Granulomatous features on histology, no./no. assessed (%)	12/14 (86)	95/209 (45)	<0.01
Ear/nose/throat	11 (73)	217 (79)	0.57
Bloody nasal discharge	10 (67)	184 (67)	>0.99
Sinus involvement	10 (67)	133 (49)	0.18
Subglottic inflammation	0 (0)	31 (11)	0.38
Hearing loss, conductive	4 (27)	61 (22)	0.70
Mucous membranes/eyes	5 (33)	94 (34)	0.93
Conjunctivitis/episcleritis	3 (20)	56 (21)	>0.99
Uveitis	0 (0)	3 (1)	>0.99
Scleritis	1 (7)	22 (8)	>0.99
Orbital mass/proptosis	1 (7)	11 (4)	0.48
Heart	0 (0)	4 (2)	>0.99
Gastrointestinal tract	0 (0)	4 (2)	>0.99
Pulmonary	10 (67)	170 (62)	0.73
Endobronchial involvement	1 (7)	28 (10)	>0.99
Nodules or cavities	5 (33)	92 (34)	0.98
Alveolar hemorrhage	1 (7)	65 (24)	0.20
Cutaneous	1 (7)	66 (24)	0.20
Renal	3 (20)	170 (62)	<0.01
GFR (MDRD), mean	76.3	66.7	0.37
Nervous system	2 (13)	44 (16)	>0.99
Sensory peripheral neuropathy	2 (13)	36 (13)	>0.99
Motor mononeuritis	1 (7)	12 (4)	0.51
Relapse rate			
Relapsing disease at trial entry	13 (87)	156 (57)	0.02
Participants with relapse at 6 months	6 (40)	71 (26)	0.23
Severe relapse	0 (0)	23 (9)	0.62
Participants with relapse at 12 months	8 (53)	127 (47)	0.61
Severe relapse	1 (7)	44 (16)	0.48
Participants with relapse at 18 months	9 (60)	148 (54)	0.66
Severe relapse	3 (20)	63 (23)	0.78

* Except where indicated otherwise, values are the number (%). See Table 1 for definitions.

MPO-ANCA–positive GPA subset. Conductive hearing loss, subglottic inflammation, orbital masses, and endobronchial involvement did not occur in patients with MPA. MPO-ANCA–positive GPA patients were less likely to have renal involvement (67% versus 86%; $P = 0.04$). Other "capillaritis-related" manifestations such as diffuse alveolar hemorrhage and vasculitic neuropathy did not differ in frequency or severity between the 2 groups.

We reviewed the records of the 9 patients with MPA who had clinical manifestations associated with GPA, including 1 patient with sinus involvement, 1 patient with pulmonary nodules, and 7 patients with bloody nasal discharge. All patients had either alveolar hemorrhage or glomerulonephritis or both. All but 1 of these patients underwent biopsy, and none of the biopsies demonstrated granulomatous features. The patient with pulmonary nodules did not have pulmonary nodules at trial entry but developed them during disease relapse.

MPO-ANCA–positive patients with GPA were more likely to have relapsing disease at trial entry than MPO-ANCA–positive patients with MPA (58% versus 18%; $P < 0.01$). In addition, MPO-ANCA–positive patients with GPA relapsed more frequently at 12 and 18 months than MPO-ANCA–positive patients with MPA (36% versus 11%; $P < 0.01$ and 45% versus 18%; $P < 0.01$, respectively). Damage as measured by the VDI did not differ between the 2 groups over the course of the trials.

ANCA-negative GPA patients versus PR3-ANCA–positive GPA patients. Fifteen patients classified by investigators as having GPA were ANCA negative by ELISA for antibodies to the PR3 and MPO

antigens. In comparison to PR3-ANCA–positive patients with GPA, ANCA-negative patients were more likely to be female (67% versus 39%; $P = 0.03$) but demonstrated a similar age distribution (Table 3). ANCA-negative patients had a lower mean BVAS/WG at entry compared to PR3-ANCA–positive GPA patients (4.5 versus 7.7; $P < 0.01$), primarily because of their lower likelihood of renal involvement (20% versus 62%; $P < 0.01$). Other "capillaritis-related" disease features such as purpura and alveolar hemorrhage were seen in only 1 ANCA-negative patient but differences did not reach statistical significance. As expected, ANCA-negative patients with GPA were more likely to undergo tissue biopsy and more likely to have granulomatous features shown on histopathology than were GPA patients who were PR3-ANCA positive. ANCA-negative patients with GPA more commonly had relapsing disease at trial entry (87% versus 57%; $P = 0.02$), but the rate of relapse during follow-up was similar in the 2 groups. Disease damage did not differ between the 2 groups.

DISCUSSION

These analyses focused on the subsets of patients with GPA who are MPO-ANCA positive and ANCA negative. Our findings suggest that while MPO-positive patients are more likely to be women, other demographic characteristics and clinical manifestations are similar across the GPA disease type. We also demonstrate that patients with GPA have a similar relapse rate across ANCA type and that MPO-ANCA–positive patients with GPA have a higher relapse rate than MPO-ANCA–positive patients with MPA. These data contribute important information to the ongoing discussion of the relative contributions of ANCA type as opposed to AAV diagnosis in the expression of disease phenotype and response to treatment (21).

Our analysis delineates important sex disparities across AAV subsets (22). MPO-ANCA–positive patients with GPA and ANCA-negative patients with GPA were more likely to be women. An earlier report from the WGET described a tendency for nonsevere (limited) GPA to occur in women (23) and is consistent with recent reports from Japan of MPO-ANCA–positive GPA patients (7,8). Our data also bring into sharper focus the subset of GPA patients who are PR3-ANCA positive. In contrast to the tendency for MPO-ANCA–positive GPA and ANCA-negative GPA to affect women, PR3-ANCA–positive GPA denotes a disease subset that more commonly affects men.

Despite the sex differences demonstrated between the MPO-ANCA–positive patients with GPA and ANCA-negative patients with GPA compared to the PR3-ANCA–positive GPA subset, no differences in age were detected across these groups. This stands in striking contrast to the finding that patients with GPA were a mean of 11.1 years younger than their MPA counterparts. This finding has also been observed by others and is consistent across ANCA types (4,24–26). Thus, regardless of ANCA type, patients with a diagnosis of GPA tend to develop their disease at a younger age than do those with diagnoses of MPA. This finding contrasts with data from a Japanese cohort which demonstrated that MPO-ANCA–positive patients with GPA tended to be older than PR3-ANCA–positive patients (8).

Despite the observations that genetic differences cluster more closely with ANCA type than disease type (1), we were unable to demonstrate differences in disease manifestations between MPO-ANCA–positive and PR3-ANCA–positive patients with GPA. In our cohort, MPO-ANCA–positive patients with GPA were similar to PR3-ANCA–positive patients with GPA with regard to all clinical features, including sino-nasal involvement, subglottic inflammation, pulmonary nodules, and renal disease. Previous publications have reported that MPO-ANCA–positive patients with GPA may have less extensive disease (6) and more frequent ear, nose, and throat involvement than PR3-ANCA–positive GPA patients (8). These differences may be due to the relatively small number of MPO-ANCA patients included (6) and the patient population under study (8) (MPO-ANCA positivity is more common in the Japanese population [27].) It should also be noted that patients with nonsevere AAV were not included in the RAVE trial, which may have affected our results.

In our cohort, MPO-ANCA–positive patients with GPA did not experience scleritis or endobronchial lesions; however, reports on other cohorts have described scleritis and endobronchial lesions in patients with pANCA and MPO-ANCA, respectively (7,28). ANCA-negative patients in our cohort also differed from PR3-ANCA–positive GPA patients in having not only less renal involvement, but also the occurrence of alveolar hemorrhage and cutaneous disease in only 1 patient each. These findings are consistent with previous reports suggesting that nonsevere or "limited" disease is more frequently ANCA negative (29).

The risk of relapse in our study was associated more closely with disease type than ANCA type. MPO-ANCA–positive patients with GPA experienced relapses at a similar rate as PR3-ANCA–positive patients with GPA. In contrast, MPO-ANCA–positive patients with

GPA had more frequent relapses than MPO-ANCA–positive patients with MPA. Although one prior study showed a similar rate of relapse in MPO- and PR3-positive patients with GPA (8), our findings contrast with those of studies suggesting that ANCA type is the predominant determinant of clinical outcomes (2,3).

The different outcome found in our study may be explained by the differences in the patient cohorts under investigation. Patients enrolled in cohort studies may differ from those enrolled in clinical trials (30). The study by Lionaki et al (3) included patients from a single nephrology center, all of whom had renal disease. Moreover, only 23% of the patients studied by Lionaki et al had GPA according to the CHCC nomenclature (23). The characteristics of the patients in that study therefore contrast sharply with those of our patient cohort, in which the predominant disease subset was patients with GPA, a group widely acknowledged to be at higher risk of relapse (7). Similarly, the cluster analysis of 5 prospective European Vasculitis Study Group trials and a French Vasculitis Study Group trial conducted by Mahr and colleagues included only patients with newly diagnosed disease (2), a subset also known to be at lower risk of relapse than the cohort of patients investigated in this study, of whom 54% had relapsing disease at study entry. Given the discordant findings in studies addressing the contribution of disease type and ANCA type to the risk of relapse in AAV, further studies including larger patient subsets should be conducted. Until then, both disease type and ANCA type may be considered in the determination of treatment strategies for the maintenance of remission and in clinical trial design.

A surprising finding in our study was that the ANCA-negative GPA patients comprised the subset most likely to have relapsing disease at entry. We cannot exclude the possibility of trial recruitment bias as the explanation for this distinction, however, and note that the relapse rate of ANCA-negative patients with GPA did not differ from that of the PR3-ANCA–positive patients with GPA during the course of follow-up in this study. This finding will require further investigation in future studies.

Our study has a number of important strengths. We analyzed data from 2 of the largest multicenter trials in AAV completed to date. These trials were characterized by robust data collection and rigorous monitoring. The subsets that comprise the principal focus of this study—the MPO-ANCA–positive and the ANCA-negative patients with GPA—form one of the largest collections of such subsets yet analyzed in the literature. Finally, all of the serum samples were analyzed for ANCA in the same laboratory at the Mayo Clinic, using both direct and capture ELISA methods, increasing the likelihood that patients were classified correctly according to their ANCA type.

The study also has certain limitations. The RAVE and WGET trials had different inclusion criteria as well as different treatment protocols. Therefore, our pooled analysis may have been affected by differing trial populations and treatment protocols, particularly with regard to relapse risk. However, the remission rates and relapse rates in the 2 trials were similar, suggesting that the trials could be pooled for analysis. We were unable to evaluate clinical outcomes such as remission maintenance, because differing trial protocols prevented the pooling of these data for analysis. Further, we were unable to evaluate the effect of different treatment regimens on clinical outcomes due to the relatively small numbers of patients in the MPO-ANCA–positive and ANCA-negative GPA subsets. This will require further study in a larger patient population.

Data on disease manifestations prior to enrollment were not available; therefore, disease manifestations that the patients had prior to study entry were not included in the analysis. We did not attempt to reclassify patients based on new clinical manifestations that developed during the course of the trials (e.g., patients with MPA who developed lung nodules). Our study had low power to detect differences in rare clinical manifestations and limited ability to detect severity of certain organ manifestations (e.g., sinus disease and peripheral neuropathy). We were also unable to analyze PR3-ANCA–positive patients with MPA because there were only 4 such patients in the 2 trials combined. PR3-ANCA–positive MPA is rare in clinical practice as well and it is difficult to conduct studies on such patients, perhaps because certainty with regard to diagnosis is challenging. Finally, ANCA-negative MPA patients were not enrolled in either the WGET or RAVE trials, and therefore were excluded from this study.

In summary, our analysis suggests that sex is more closely associated with ANCA type, but that patient age, clinical manifestations, and risk of relapse are more closely associated with disease type in our patient subset. Analyzing MPO-ANCA–positive patients with GPA and ANCA-negative patients with GPA contributes new findings to the debate on the importance of disease type versus ANCA type classifications within AAV. These 2 distinct patient subsets warrant further study.

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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