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Predictors of Treatment Resistance and Relapse in Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis:

Comparison of Two Independent Cohorts

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Abstract

Objective—Predictors of treatment resistance and relapse have been identified in patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis in the Glomerular Disease Collaborative Network (GDCN) in the southeastern US. This study was undertaken to evaluate the applicability of those predictors in an independent cohort followed up by the French Vasculitis Study Group.

Methods—Predictors of treatment resistance were evaluated using logistic regression models and reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). Predictors of relapse were evaluated using Cox proportional hazards models and reported as hazard ratios (HRs) with 95% CIs. Models were controlled for age, sex, race, baseline serum creatinine level, and cyclophosphamide therapy.

Results—The French cohort (n = 434) and the GDCN cohort (n = 350) had similar median followup periods (44 months versus 45 months) and initial percentages of patients taking cyclophosphamide (82% versus 78%). The French cohort included more patients with proteinase 3 (PR3) ANCA (58% versus 40%), lung involvement (58% versus 49%), and upper respiratory tract involvement (62% versus 31%). Of the predictors of treatment resistance in the GDCN cohort (female sex, African American race, presence of myeloperoxidase ANCA, elevated creatinine level, and age), only age predicted treatment resistance in the French cohort (OR 1.32 per 10 years [95% CI 1.05–1.66]). Predictors of relapse in the GDCN cohort were PR3 ANCA (HR 1.77 [95% CI 1.11–2.82]), lung involvement (HR 1.68 [95% CI 1.10–2.57), and upper respiratory tract involvement (HR 1.58 [95% CI 1.00–2.48]), while predictors in the French cohort were PR3 ANCA (HR 1.66 [95% CI 1.15–2.39]) and lung involvement (HR 1.56 [95% CI 1.11–2.20]), but not upper respiratory tract involvement (HR 0.96 [95% CI 0.67–1.38]).

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AUTHOR CONTRIBUTIONS

Dr. Nachman 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 design. Pagnoux, Hogan, Jennette, Falk, Guillevin, Nachman.
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Conclusion—Our findings indicate that older age is a predictor of treatment resistance, and that PR3 ANCA and lung involvement are predictors of relapse in both cohorts. Discrepancies in predictors of treatment tract resistance may reflect differences in access to care, and differences in predictors of relapse may reflect variations in disease expression.

Diseases classified as antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis include microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), and renal-limited vasculitis ANCA-associated glomerulonephritis) (1,2). The cornerstone of treatment for ANCA vasculitis includes induction therapy with corticosteroids and intravenous (IV) or daily oral cyclophosphamide (3–6). The majority of patients respond well to this therapy; remission is achieved in ~85% of patients (5,7–9). Unfortunately, 11–57% of patients experience a relapse (8,10–13). Some relapses are severe and may result in worsening end-organ damage. Most relapses respond to therapy, but patients must receive repeated courses of immunosuppressive or cytotoxic drugs.

Fear of relapsing disease has resulted in physicians prescribing prolonged maintenance therapies to the majority of patients. However, because approximately half of the patients may never have a disease relapse (8,10–13), long-term use of immunomodulating therapy will often result in unnecessary treatment and therapy-related risks that may outweigh the benefits of preventing relapse. Knowledge of risk factors for relapse is critical for tailoring the use of maintenance immunomodulating therapy to patients at high risk, while sparing those at low risk from receiving unnecessary therapy.

Predictors of treatment resistance and relapse were identified in a large cohort of patients (n = 350) with ANCA-associated glomerulonephritis and ANCA vasculitis recruited over almost 2 decades and followed up prospectively within the Glomerular Disease Collaborative Network (GDCN), based in the southeastern US (7). In multivariable analysis, therapy-resistant disease (found in 29% of the patients) was associated with female sex, African American ethnicity, older age, and the severity of renal disease at presentation, while relapse (experienced by 42% of the patients) was independently predicted by the presence of proteinase 3 (PR3) ANCA, and disease involvement of the lungs and upper respiratory tract. Of patients who presented without any of the 3 risk factors for relapse, 26% experienced a relapse in a median of 62 months, while of those who had ≥1 risk factor, 47% experienced a relapse in a median of 39 months, which corresponded to a 2-fold increased risk of relapse (95% confidence interval [95% CI] 1.1–3.9) (P = 0.038). The present study was undertaken to assess whether the risk factors for resistance to therapy and disease relapse identified in the GDCN cohort were applicable in an independent cohort of patients with ANCA vasculitis followed up by the French Vasculitis Study Group (FVSG).

PATIENTS AND METHODS

Patients

The French cohort (n = 533) included patients with ANCA vasculitis diagnosed between 1970 and February 2006 at more than 100 university and general hospitals throughout France. Patients were identified for the study when they were enrolled in one of the FVSG single-center or multicenter trials or when referred to the Internal Medicine Department at Bobigny, France until 2003, and thereafter to the French National Referral Center for Necrotizing Vasculitides, Department of Internal Medicine, Hôpital Cochin. Data were compiled in a standardized form in a centralized registry at the French National Referral Center for Systemic Vasculitides. Patients were invited to participate via their treating physician, and written informed consent was obtained from all patients. Followup was conducted through phone calls to patients and/or their physicians, starting in 1980. The patient registry and database were approved for

research purposes by the Commission Nationale de l'Informatique et des Libertés (Paris, France).

Patients with ANCA vasculitis in the US cohort (n = 350) were diagnosed between 1985 and 2003 and followed up by physicians in the GDCN, which included 63 private practice offices and 5 academic medical centers (7). Methods of identifying and enrolling patients have been described previously (7). Briefly, patients were primarily identified for the study through the University of North Carolina (UNC) Nephropathology Laboratory. Therefore, most of the patients (n = 307) had biopsy-proven renal involvement in ANCA vasculitis (pauci-immune necrotizing and crescentic glomerulonephritis). Forty-three patients who had not undergone renal biopsy were recruited through the multidisciplinary UNC Vasculitis Clinic and by other GDCN nephrologists who collaborate with various medical specialists who care for patients with ANCA vasculitis. The GDCN study was approved by The UNC Committee on the Protection of Human Subjects.

To be included in the study, patients in both cohorts had to be positive for ANCA, as determined by immunofluorescence microscopy and/or antigen-specific enzyme-linked immunosorbent assay (14). Patients were categorized as having cytoplasmic and/or PR3 ANCA or perinuclear and/or myeloperoxidase ANCA (MPO ANCA). Patients who had perinuclear ANCA alone had to be negative for antinuclear antibodies in order to be included in the study. Patients with target antigen specificities to both MPO and PR3 were excluded, because it was not possible to assess the effect of PR3 ANCA on the risk of relapse.

Diagnostic categories

Diagnostic categories included WG, MPA, and renal-limited disease (1,2). Patients with features of polyarteritis nodosa (PAN) or giant cell arteritis (GCA) were excluded if the diagnosis of small-vessel arteritis could not be confidently established (n = 16 in the French cohort and 0 in the GDCN cohort). Patients with CSS were excluded from both cohorts due to their small number in the GDCN cohort (n = 69 in the French cohort and 3 in the GDCN cohort). Furthermore, the character of pulmonary involvement (asthma) and its high frequency (>85%) in patients with CSS, and the difficulties in assessing pulmonary relapses in these patients (15,16), would significantly skew the assessment of the impact of pulmonary disease on relapse.

Organ involvement was determined by biopsy or by previously described criteria (4,8). Lung involvement was considered likely in the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, or radiography-proven infiltrates, nodules, or cavities without evidence of infection. Upper respiratory tract disease was considered likely when clinical evaluation or radiography revealed sinusitis, otitis media, nasal crusting, and/or subglottic disease.

Treatment categories

Treatment categories were based on the first therapy regimen used at diagnosis. In the French cohort, therapeutic interventions and the frequency of clinical evaluations were determined by protocol for 325 of the patients, who were enrolled in 13 therapeutic trials (Figure 1A). The remaining 109 patients were treated according to standard practice in France. Briefly, induction therapy was typically initiated with pulse methylprednisolone 3 times daily (7.5–15 mg/kg/day), followed by daily oral prednisone starting at 1 mg/kg for the first month, and tapered progressively over 12–24 months. A group of 48 (11%) of the French patients, all of whom had MPA without risk factors for poor outcome according to the “5-factor score” (17), were treated with corticosteroids alone. Seventeen (4%) of the patients received no treatment. All other patients were treated with cyclophosphamide (82%, n = 356) or other immunosuppressants (3%, n = 13) in addition to corticosteroids (Table 1). IV pulse

cyclophosphamide (600 mg/m^2 on days 1, 15, and 30, followed by 700 mg/m^2 every 3 weeks) was given until remission (followed by 3 additional doses of pulse cyclophosphamide for response consolidation) or less frequently in the form of daily oral cyclophosphamide (2 mg/kg/day).

Patients in the GDCN cohort were treated with corticosteroids alone (13%, n = 46) or in combination with cyclophosphamide (78%, n = 270) or other immunosuppressants (4%, n = 15), while a few patients (5%, n = 16) presented with advanced renal disease and were not treated (Table 1) (3). Induction therapy was typically initiated with pulse methylprednisolone 3 times daily (7 mg/kg/day) followed by daily oral prednisone. Prednisone was started at a dose of 1 mg/kg for the first month, and tapered progressively over 3–4 months. Cyclophosphamide was administered monthly either by IV pulse (0.5–1 gm/m^2) or orally (1–2 mg/kg/day). Other immunosuppressive agents used in both cohorts included azathioprine, methotrexate, and mycophenolate mofetil. These treatments were most commonly used after completion of induction therapy.

Primary outcomes included treatment resistance, remission on or off therapy, and relapse (4, 8). Patients who were not treated were excluded from the evaluation of predictors of resistance and relapse. Treatment resistance was defined as a progressive decline in kidney function with persistence of active urine sediment, or persistence or new appearance of any extrarenal manifestations of active vasculitis despite immunosuppressive therapy. The determination that a patient had disease that was resistant to therapy was made at least 1 month after the start of treatment. Remission was defined as stabilization or improvement of kidney function, as measured by the serum creatinine level and resolution of hematuria and other manifestations of systemic vasculitis, for >1 month. Relapse could occur only in patients in whom remission was reached (on or off therapy). Relapse was defined as the presence of signs or symptoms of significant vasculitis in any organ system, as previously described (4,8).

Statistical analysis

Comparisons between cohorts for continuous measures were performed using *t*-tests or nonparametric Wilcoxon rank sum tests. Categorical measures were compared using chi-square tests. Predictors of treatment resistance were evaluated in each cohort separately using logistic regression, and results are expressed as odds ratios (ORs) with 95% CIs and *P* values. A time-to-event analysis was not performed for treatment resistance, since the actual time to resistance is not known, and because this outcome occurs within a short time. Cox proportional hazards models were used to evaluate time to relapse within each cohort, and results are expressed as hazard ratios (HRs) with 95% CIs and *P* values. Patients who died or reached end-stage kidney disease at the time of an active relapse were considered to have experienced a relapse. Patients were censored if they had not experienced a relapse at their last followup. Patients who died without evidence of disease activity were censored on the date of death. The proportional hazards assumption was assessed by examining plots of both log(–log S(t)) and Schoenfeld residuals (18,19).

Demographic and other variables assessed as potential predictors of treatment resistance and relapse in the GDCN cohort were determined in the previous study (7) (Table 1). The predictors of treatment resistance and relapse found in the GDCN cohort were evaluated in the French cohort using multivariable models controlling for the same variables. Treatment was controlled for in all models, as corticosteroids alone versus corticosteroids plus cyclophosphamide or other immunosuppressants. SAS version 8.2 software (SAS Institute, Cary, NC) was used for statistical analysis (20).

RESULTS

Description of the cohorts

The original French cohort included 533 patients who were followed up prospectively. In addition to the 69 patients with CSS who were excluded, 30 patients were excluded due to lack of outcome information (n = 2), unknown ANCA specificities (n = 3), dual ANCA specificities (n = 9), or features of PAN or GCA (n = 16). A total of 434 patients in the French cohort were therefore analyzed in the present study (Figure 1A). The GDCN cohort (Figure 1B) has been described in detail previously (7). Of the 350 patients previously evaluated, 3 with CSS were excluded from the current analysis.

Characteristics of the patients in the French and GDCN cohorts are summarized in Table 1. With respect to demographic characteristics, the numbers of men and women in each cohort were similar, but patients in the French cohort were younger (median age 57 years) than patients in the GDCN cohort (median age 63 years). Both cohorts consisted primarily of white patients, although the GDCN cohort included a larger proportion of patients of African descent (9% versus 1%; $P < 0.0001$) (Table 1). PR3 ANCA positivity was more common among patients in the French cohort than in the GDCN cohort (58% versus 40%; $P < 0.0001$).

Diagnosis categories and organ involvement were markedly different between the cohorts, with a predominance of patients with WG in the French cohort (66% versus 17% in the GDCN cohort) and far more frequent pulmonary and upper respiratory tract involvement in the French cohort (58% and 62%, respectively) than in the GDCN cohort (49% and 31%, respectively) (Table 1). Conversely, the GDCN cohort had a predominance of patients with MPA and kidney-limited disease (57% and 26%, respectively), and 88% of the patients had kidney involvement. This was markedly different from the French cohort, in which 33% of the patients had MPA, 1% had kidney-limited disease, and 71% had kidney involvement (Table 1). The differences with respect to the kidney were also reflected in the more severe renal dysfunction seen at presentation in the GDCN cohort than in the French cohort (mean ± SD serum creatinine level 422 ± 324 μmoles/liter versus 193 ± 211 μmoles/liter [$P < 0.0001$]).

Importantly, the 2 cohorts were similar with respect to therapy, with only minimal differences between the French and GDCN cohorts in the proportion of patients treated with corticosteroids alone (11% versus 13%), cyclophosphamide plus corticosteroids (82% versus 78%), or other immunosuppressive agents plus corticosteroids (3% versus 4%). Four percent of the patients in the French cohort and 5% of the patients in the GDCN cohort received no immunosuppressive treatment. Median followup time was similar in the French and GDCN cohorts (44 and 45 months, respectively [$P = 0.69$]).

Comparison of outcomes in the French and GDCN cohorts

Of the 417 patients in the French cohort who were treated, disease was resistant to therapy in 58 (14%) of the patients (Figure 1A). A response to initial treatment occurred in 359 patients (86%). Of these 359 patients, remission was achieved and sustained with or without maintenance therapy in 166 patients (46%) for a median of 106 months, while 193 patients (54%) experienced a relapse over a median of 44 months (the median time to relapse among those who relapsed was 30 months) after beginning therapy (Table 1).

The initial response to treatment was different between the cohorts (Table 1), with a higher percentage of treatment-resistant disease in treated patients in the GDCN cohort (76 of 331 patients [23%] versus 14% in the French cohort) ($P = 0.0013$). Of the 255 GDCN patients in whom remission was achieved, 106 (42%) experienced a relapse over a median of 45 months (the median time to relapse among those who relapsed was 16 months) after beginning therapy. In comparison, of the 359 French patients in whom remission was achieved, 193 (54%) ($P =$

0.003) experienced a relapse over a median of 44 months ($P = 0.57$). When the analysis of time to relapse was limited to patients in each cohort who did experience a relapse, the median time to relapse was shorter in the GDCN cohort than in the French cohort (16 months versus 30 months [$P = 0.0009$]).

Predictors of treatment resistance

Based on findings obtained in the GDCN cohort, the following risk factors for treatment resistance were identified: female sex (OR 1.84 [95% CI 1.02–3.33], $P = 0.044$), African American race (OR 3.10 [95% CI 1.19–7.85], $P = 0.013$), older age (OR per 10 years 1.21 [95% CI 1.00–1.47], $P = 0.046$), and an elevated serum creatinine level, with each increment of 100 μmoles/liter associated with a 1.22 OR of resistance (95% CI 1.12–1.34) ($P < 0.001$) (7) (Table 2). In the French cohort, age was a statistically significant predictor of treatment resistance (OR per 10 years 1.32 [95% CI 1.05–1.66], $P = 0.018$), but sex, race, and increasing serum creatinine level were not.

Overall, results were similar when the evaluation of each cohort was limited to cyclophosphamide-treated patients only, with 3 exceptions. The associations of increasing age per 10 years and of sex with treatment resistance were attenuated and no longer statistically significant in the GDCN cohort (OR 1.15 [95% CI 0.92–1.45], $P = 0.227$ and OR 1.62 [95% CI 0.82–3.21], $P = 0.168$, respectively), whereas age remained a risk factor for treatment resistance in the French cohort (OR 1.35 [1.06–1.72], $P = 0.016$). In the French cohort, the impact of increasing serum creatinine level (per 100 μmoles/liter) approached significance (OR 1.12 [95% CI 0.99–1.26], $P = 0.070$).

Predictors of relapse

In the GDCN cohort (7), among the 255 patients in whom remission was achieved, those with PR3 ANCA were 1.77 times more likely to experience a relapse than were patients with MPO ANCA (95% CI 1.11–2.82) ($P = 0.017$) (Table 3). Lung involvement was associated with an increased risk of relapse (HR 1.68 [95% CI 1.10–2.57], $P = 0.017$), as was upper respiratory tract involvement (HR 1.58 [95% CI 1.00–2.48], $P = 0.048$). The overlap of these 3 risk factors among patients in whom remission was attained, and were therefore able to experience a relapse, is shown in Figure 2A for the French cohort and Figure 2B for the GDCN cohort. In the French cohort, 80% of the patients had 2 or more of these risk factors, and in the GDCN cohort, 63% of the patients had 2 or more risk factors.

Of these 3 risk factors, PR3 ANCA was associated with a 1.66-fold increased risk of relapse in the French cohort (95% CI 1.15–2.39) ($P = 0.006$), and lung involvement was associated with a 1.56-fold increased risk of relapse (95% CI 1.11–2.20) ($P = 0.010$). These associations were independent of age, sex, race, serum creatinine level, treatment with immunosuppressants, and each of the other risk factors. In contrast, the presence of upper respiratory tract disease was not a predictor of relapse in the French cohort (HR 0.96 [95% CI 0.67–1.38], $P = 0.820$) (Table 3). Of note, only 23 (10%) of 226 patients with upper respiratory tract disease in the French cohort who responded to treatment did not have one of the other 2 risk factors, versus 17 (19%) of 90 patients in the GDCN cohort (Figure 2). The presence of both lung involvement and PR3 ANCA antibodies had a synergistic effect on the risk of relapse in the GDCN cohort (HR 2.46 [95% CI 1.60–3.77], $P < 0.0001$), but not in the French cohort (HR 1.57 [95% CI 1.13–2.18], $P = 0.007$) (Table 3). When the evaluation of each cohort was limited to cyclophosphamide-treated patients, the results were analogous, although the confidence intervals were slightly wider given the smaller sample size (data not shown).

DISCUSSION

Because 40–50% of patients with ANCA vasculitis experience relapse, long-term maintenance therapy with immunosuppressive agents is commonly used in the hope of limiting the incidence and severity of relapses. Unfortunately, controlled evidence that maintenance therapy is effective in attaining this objective remains limited and inconclusive (21). Furthermore, immunosuppressants currently used for maintenance therapy are associated with risks of infection and malignancy. Therefore, the impetus for stratifying patients according to their risk of relapse is to optimize the risk/benefit ratio of long-term immunosuppression by targeting patients at high risk of relapse, while avoiding giving unnecessary treatment to those at low risk.

The risk factors of relapse previously identified in the GDCN cohort of patients with ANCA vasculitis (7) (lung disease, upper respiratory tract involvement, and the presence of PR3 ANCA) were determined based on simple, objective clinical observations and a blood test. Because the GDCN cohort comprised primarily patients referred to nephrologists, a perceived limitation of that study was that the results could be skewed by an overrepresentation of patients with renal disease and may not apply to patients representing a broader spectrum of ANCA vasculitis. The aim of the present analysis was, therefore, to evaluate the applicability of the 3 risk factors in predicting relapse in a large, independent patient cohort, prospectively collected and followed up by the FVSG. However, for these risk factors to be truly validated, they would need to be assessed as part of a prospective study with uniform induction and maintenance treatment protocols, and duration of followup sufficiently prolonged to evaluate rates of relapse.

The GDCN and French cohorts were comparable with regard to sex, but patients in the French cohort were younger, and the ethnic distribution differed slightly between the cohorts, although both were largely white. There were also differences in the proportions of patients with organ involvement and in diagnostic categories. Indeed, the differences in organ involvement were likely due in part to the referral bases for the 2 cohorts. The FVSG is primarily composed of internists or rheumatologists, whereas the GDCN is primarily composed of nephrologists, resulting in a cohort that is skewed toward a predominance of patients with renal disease. However, there could be a true underlying difference in the distribution of phenotypes between the 2 geographic regions, as has been previously described, with a higher proportion of patients with WG in the higher latitudes (43–49° in France) and a higher proportion of patients with MPA in lower latitudes (32–37° in the southeastern US) (22–24).

Although clinicians evaluating diagnostic categories used the same criteria (1), we cannot exclude the potential for differences in the frequency of diagnosis of WG based on the presence of upper respiratory tract disease. In the GDCN cohort, patients with severe destructive sinusitis and/or subglottic stenosis were diagnosed as having WG, whereas patients with milder involvement without clear clinical evidence of granulomatous disease were diagnosed as having MPA. In comparison, the latter patients were more likely to be diagnosed as having WG in the French cohort. These differences highlight the difficulties and nuances in ascribing diagnoses, and in basing comparative analyses on diagnosis rather than objective description of organ involvement.

Age was associated with an increased rate of treatment resistance in both the French and GDCN cohorts. This increased risk of resistance may be due to the presentation of older patients with a lower glomerular filtration rate due to age and chronic underlying comorbid conditions, such as hypertension. Alternatively, there is a tendency to treat older patients with lower doses of immunosuppressants because of increased risk of bone marrow suppression, leukopenias, and infections (25). The optimal treatment for older patients, given the risks and benefits of

"standard" versus reduced doses of cyclophosphamide and corticosteroids, is currently being addressed in the ongoing Treatment of Necrotizing Vasculitides for Patients Older Than 65 Years (CORTAGE) study (www.clinicaltrials.gov study identifier: NCT00307671; www.vascularites.org).

In the GDCN cohort, African American race and female sex were identified as risk factors for treatment resistance. These findings were not confirmed in the French cohort. The reason for this difference is unclear. We suspect that in the US, differences in socioeconomic status and access to health care contribute to the lower response rates among minorities and possibly among women and the elderly. Even when insurance is taken into consideration or only managed care enrollees are studied, US minorities and women lag behind white men in numerous health-related issues, including disease screenings, management, and outcomes (26–29). The finding that age and sex were not predictive of treatment resistance in the subgroup analysis of cyclophosphamide-treated patients in the GDCN cohort supports the notion that appropriate treatment may obviate some of the disparities among these demographic groups. The fact that sex and race were not statistically significant predictors of treatment resistance in France may reflect more uniform access to care.

The impact of renal dysfunction on treatment resistance seen in the GDCN cohort was not confirmed in the French cohort. This is likely because the French cohort included fewer patients with kidney disease in general and severe renal failure in particular (Table 1). When analysis of the French cohort was limited to patients treated with cyclophosphamide, increasing renal function impairment approached statistical significance as a predictor of treatment resistance. Since the FVSG systematically used corticosteroids alone for patients without risk factors for poor outcome according to the "5-factor score," which includes renal involvement (17), the cyclophosphamide-treated group included patients with a wider range of renal involvement, more similar to the GDCN cohort. Some patients presenting with severely impaired glomerular filtration rate have already sustained chronic irreversible glomerular and interstitial scarring and do not respond to immunosuppressive therapy. In the GDCN cohort, such patients frequently fell into the category of patients presenting with renal-limited disease, associated with MPO ANCA (7). This association likely explains in part why MPO ANCA was found to be a risk factor for treatment resistance in the GDCN cohort but not in the French cohort, which included very few such patients.

The fact that lung disease and PR3 ANCA were predictive of relapse in both cohorts, despite the differences in their prevalence, emphasizes the strength of these factors as predictors of relapse. In our analysis of lung disease, we did not distinguish between granulomatous (nodules or cavities) and vasculitic (capillaritis with pulmonary hemorrhage) forms. An association between lung involvement and relapse was previously demonstrated in 1 of 2 studies of WG (30,31). The finding of PR3 ANCA as a predictor of relapse has also been reported previously (32).

The major difference in terms of predictors of relapse between the 2 cohorts was the fact that upper respiratory tract disease was not a predictor of relapse in the French cohort. This difference may reflect several factors. First, there are difficulties in distinguishing a relapse from infectious or allergic disease when the changes in upper respiratory tract symptoms are small. Therefore, a relapse in upper respiratory tract disease is not as easily definable as a relapse of disease in other organs (e.g., the lungs or kidneys). Second, upper respiratory tract involvement is frequently the site of "grumbling" long-term disease, making the diagnosis of a relapse more difficult to ascertain. Third, the high prevalence of upper respiratory tract involvement in the French cohort (62% versus 31% in the GDCN cohort) may mask the impact of this factor on the risk of relapse. Finally, there were significant differences in the distribution and overlap of the 3 risk factors between the 2 cohorts. In the French cohort, the presence of

upper respiratory tract disease overlapped to a much greater degree with the other 2 risk factors than in the GDCN cohort (Figure 2), thus limiting our ability to assess the impact of multiple versus single risk factors on relapse.

Upper respiratory tract disease per se had not been reported as a risk factor for relapse prior to the analysis of the GDCN cohort. However, upper airway colonization with *Staphylococcus aureus* has been associated with a higher relapse rate in patients with WG (33–35). The statistically significant higher rate of relapse in the French cohort compared with that in the GDCN cohort (54% versus 42%; $P = 0.003$) (Table 1), is likely attributable to the increased proportion of patients with PR3 ANCA and pulmonary disease involvement. The reason for the observed longer time to relapse among patients who experienced a relapse in the French cohort (30 versus 16 months) is unknown. It may reflect a more systematic or longer use of maintenance immunosuppressive therapy.

The GDCN and French cohorts were similar in many demographic and therapeutic aspects, yet there were significant differences with respect to the frequency of organ involvement and the severity of kidney disease. These differences likely account for the different effects of the previously identified risk factors for resistance and relapse. Several reports have described different clinical and/or pathologic risk factors for treatment resistance and relapse (17,21, 31,35,36). Our study highlights the important impact of relatively subtle differences in the composition of patient population on identifying risk factors in disease outcome, especially when studying syndromes that present with protean manifestations. Conversely, because of the differences between the French and GDCN cohorts, our study emphasizes the consistency and strength of PR3 ANCA and lung involvement as predictors of relapse in ANCA vasculitis.

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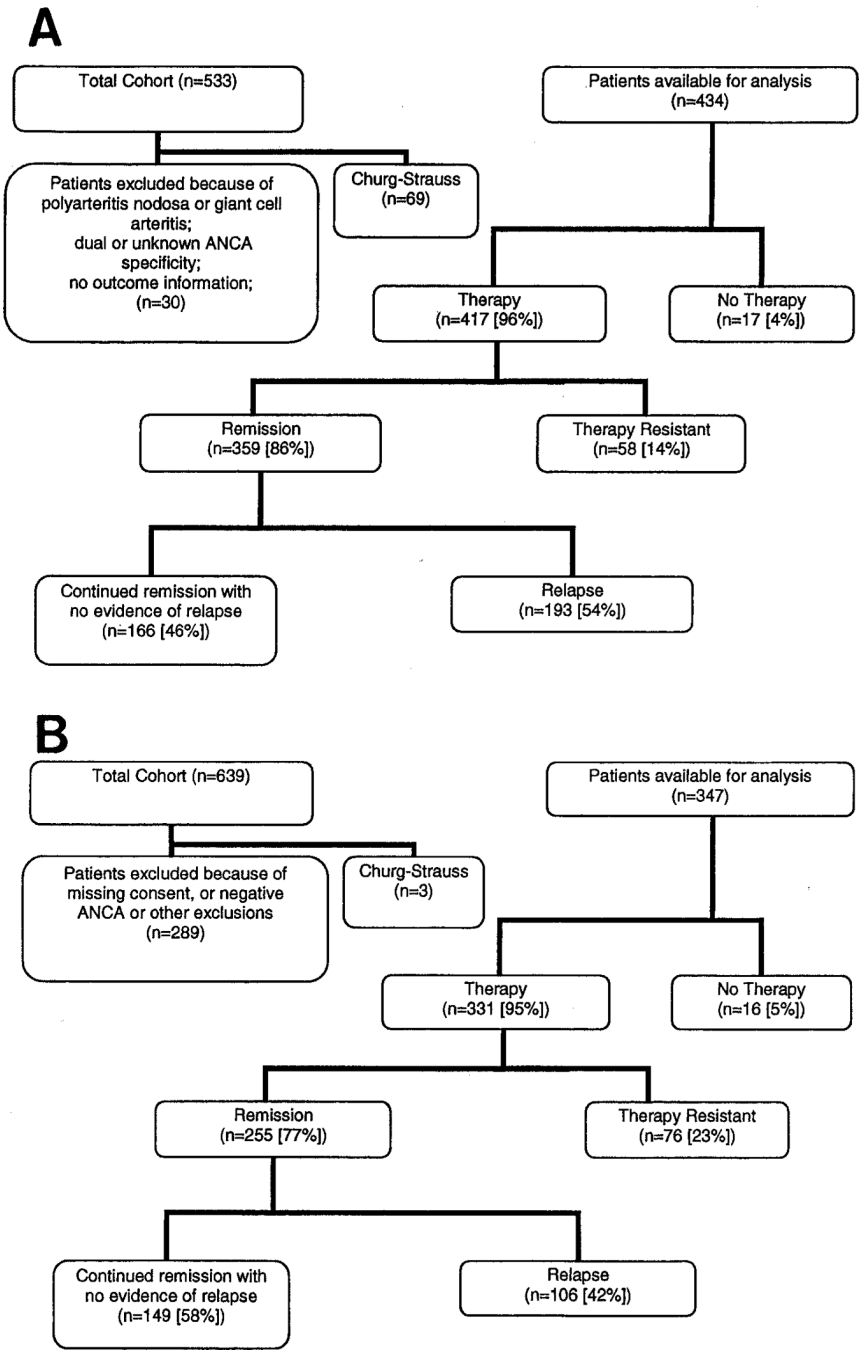

Figure 1.

Disposition of **A**, the French patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis followed up by the French Vasculitis Study Group and **B**, the US patients with ANCA vasculitis in the Glomerular Disease Collaborative Network.

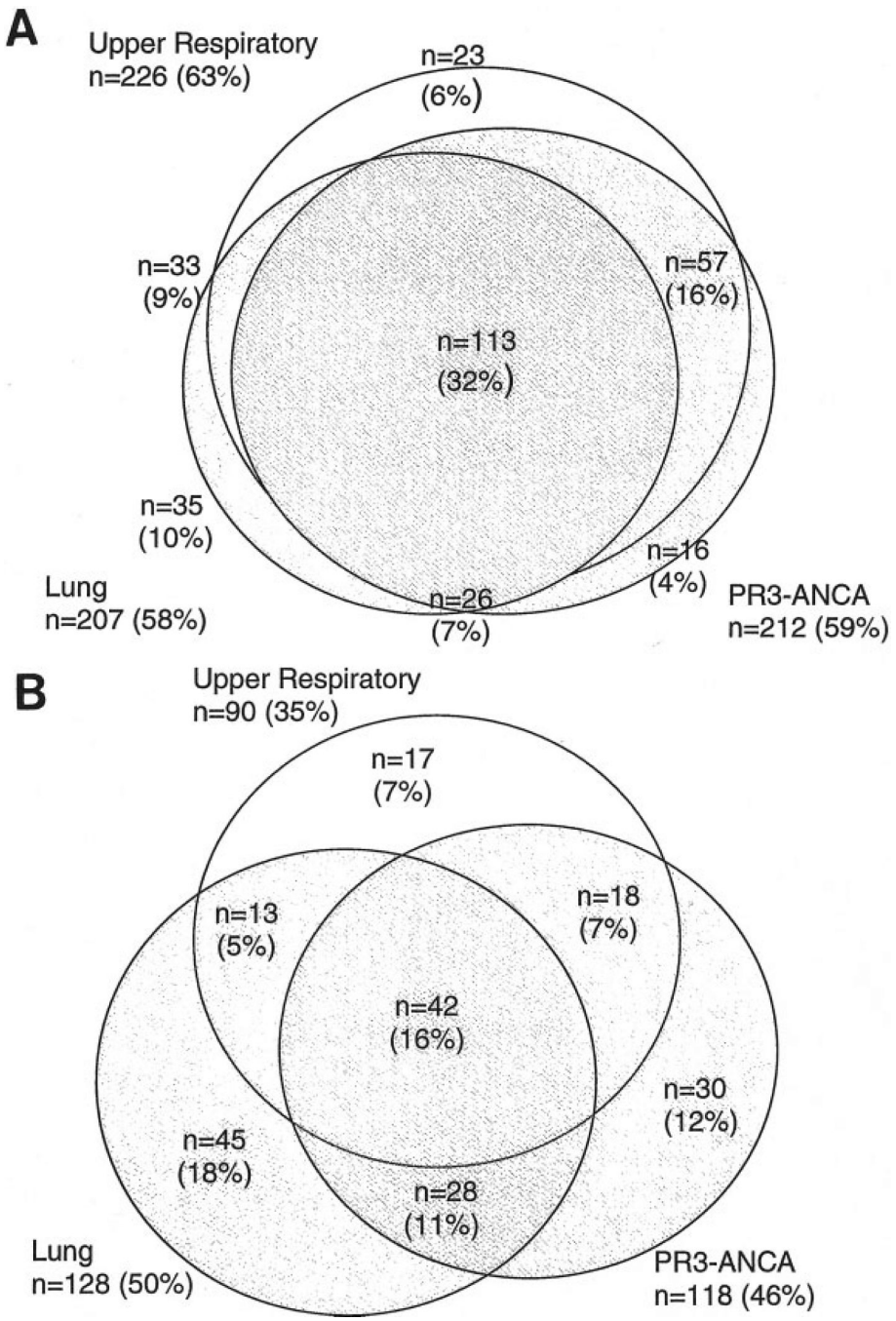

Figure 2.
Distribution of risk factors for relapse in **A**, the 359 patients in the French cohort and **B**, the 255 patients in the GDCN cohort in whom remission was achieved. PR3 ANCA = proteinase 3 antineutrophil cytoplasmic antibody.

Table 1

Characteristics of the GDCN and French ANCA vasculitis cohorts*

	GDCN cohort (n = 347)	French cohort (n = 434)	*P*
Age, years			
Mean ± SD	58 ± 18	56 ± 15	0.0009
Median (range)	63 (2–92)	57 (2–87)	–
Men	183 (53)	237 (55)	0.60
African American	33 (9)	6 (1)	<0.0001
White	311 (90)	409 (94)	0.0169
PR3 ANCA seropositive†	140 (40)	252 (58)	<0.0001
Median followup, months	45	44	0.69
Diagnosis			<0.0001
Wegener's granulomatosis	59 (17)	285 (66)	
Microscopic polyangiitis	199 (57)	143 (33)	
Kidney-limited disease	89 (26)	6 (1)	
Organ involvement			
Kidney	305 (88)	308 (71)	<0.0001
Lung	169 (49)	253 (58)	0.0075
Upper respiratory tract	106 (31)	270 (62)	<0.0001
Skin	87 (25)	162 (37)	0.0003
Serum creatinine level, μmoles/liter			
Mean ± SD	422 ± 324	193 ± 211	<0.0001
Median (range)	327 (44–1,909)	107 (45–1,730)	–
Treatment			0.50
Corticosteroids alone	46 (13)	48 (11)	
Cyclophosphamide plus corticosteroids	270 (78)	356 (82)	
Other immunosuppressant plus corticosteroids	15 (4)	13 (3)	
No treatment	16 (5)	17 (4)	
Patients with ≥1 risk factor for relapse	224 (65)	337 (78)	<0.0001
Outcome			
Treatment resistance‡	76 (23)	58 (14)	0.0013
Remission	255 (77)	359 (86)	0.0013
Relapse§	106 (42)	193 (54)	0.003
Overall median time to relapse, months	45	44	0.57
Median time to relapse among patients experiencing relapse, months	16	30	0.0009

*Except where indicated otherwise, values are the number (%) of patients.

†The group of patients with proteinase 3 antineutrophil cytoplasmic antibody (PR3 ANCA) included those with PR3 and/or cytoplasmic ANCA.

‡In the Glomerular Disease Collaborative Network (GDCN) cohort, 331 patients were treated; in the French cohort, 417 patients were treated.

§Percentages of patients who experienced a relapse are based on the numbers of patients in whom remission was achieved (255 in the GDCN cohort and 359 in the French cohort).

Table 2

Multivariable predictors of treatment resistance in the GDCN and French ANCA vasculitis cohorts*

	GDCN cohort (n = 331)		French cohort (n = 417)	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age, per 10 years	1.21 (1.00–1.47)	0.046	1.32 (1.05–1.66)	0.018
Female vs. male sex	1.84 (1.02–3.33)	0.044	1.06 (0.58–1.94)	0.862
White vs. nonwhite	0.47 (0.20–1.14)	0.097	2.06 (0.26–16.66)	0.498
PR3 ANCA vs. MPO ANCA antibody status†	0.60 (0.31–1.19)	0.144	1.24 (0.49–3.12)	0.650
WG vs. kidney-limited disease (GDCN) or MPA (French)	0.44 (0.11–1.80)	0.253	1.17 (0.41–3.29)	0.773
MPA vs. kidney-limited disease (GDCN)	0.64 (0.26–1.55)	0.318	–	–
Lung involvement	1.89 (0.86–4.17)	0.116	1.25 (0.66–2.37)	0.489
Upper respiratory tract involvement	0.84 (0.38–1.88)	0.675	0.62 (0.30–1.28)	0.191
Skin involvement	0.96 (0.45–2.05)	0.915	0.64 (0.33–1.24)	0.185
Serum creatinine level, per 100 μmoles/liter‡	1.22 (1.12–1.34)	<0.001	1.10 (0.98–1.24)	0.113

*Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression. Both cohorts were controlled for therapy (cyclophosphamide plus corticosteroids versus corticosteroids alone). GDCN = Glomerular Disease Collaborative Network; WG = Wegener's granulomatosis; MPA = microscopic polyangiitis.

†The group of patients with proteinase 3 antineutrophil cytoplasmic antibody (PR3 ANCA) included those with PR3 and/or cytoplasmic ANCA; the group of patients with myeloperoxidase (MPO) ANCA included those with MPO and/or perinuclear ANCA.

‡Level at diagnosis.

Table 3

Multivariable predictors of relapse in the GDCN and French ANCA vasculitis cohorts*

	GDCN cohort (n = 255)		French cohort (n = 359)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
PR3 ANCA vs. MPO ANCA antibody status	1.77 (1.11–2.82)	0.017†	1.66 (1.15–2.39)	0.006†
Lung involvement	1.68 (1.10–2.57)	0.017†	1.56 (1.11–2.20)	0.010†
Upper respiratory tract involvement	1.58 (1.00–2.48)	0.048†	0.96 (0.67–1.38)	0.820†
Lung involvement and PR3 ANCA vs. MPO ANCA antibody status	2.46 (1.60–3.77)	<0.0001‡	1.57 (1.13–2.18)	0.007‡

*Hazard ratios (HRs) and 95% CIs were estimated using proportional hazards models. The group of patients with PR3 ANCA included those with PR3 and/or cytoplasmic ANCA; the group of patients with MPO ANCA included those with MPO and/or perinuclear ANCA. See Table 2 for other definitions.

†Controlled for age, sex, race, serum creatinine level, therapy (immunosuppressants plus corticosteroids versus corticosteroids alone), and each of the other risk factors (antibody status, lung disease, and upper respiratory tract involvement).

‡Controlled for age, sex, race, serum creatinine level, and therapy (immunosuppressants plus corticosteroids versus corticosteroids alone).