

# Treatment Response and Relapse in Antineutrophil Cytoplasmic Autoantibody-Associated Microscopic Polyangiitis and Glomerulonephritis<sup>1,2</sup>

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## ABSTRACT

In this study, the rate of remission, relapse, and treatment resistance in 107 patients with microscopic polyangiitis and necrotizing and crescentic glomerulonephritis associated with antineutrophil cytoplasmic autoantibodies were assessed. Patients with Wegener's granulomatosis were excluded. Prospective criteria were identified to assess remission, relapse, and resistant disease. Ninety-seven of the 107 patients received treatment with corticosteroids ( $N = 25$ ) or with cyclophosphamide and corticosteroids ( $N = 72$ ). Of these patients, 75 (77.3%) went into remission (complete remission,  $N = 61$ ; remission on therapy,  $N = 14$ ). Of the 75 responders, 32 patients (43%) remained in long-term remission, for a mean follow-up of  $44 \pm 29$  months; 15 patients (20%) progressed to ESRD without signs of relapse, for a mean of  $21.4 \pm 22.8$  months after the end of treatment; 6 patients died. Twenty-two of the 75 patients who initially responded to treatment (29%) suffered a relapse that occurred within 18 months of the end of therapy and usually affected the same organ systems as on initial presentation. There was a significant difference in the remission rate between the corticosteroid-treated patients and the cyclophosphamide-treated patients (56% versus 84.7%,  $P = 0.003$ ), and the cyclophosphamide-treated patients had three times less risk of experiencing a relapse than did corticosteroid-treated patients (0.31, 95% CI = (0.12, 0.84)). Seventy-seven percent (17 of 22 patients) of treatment resistance occurred in patients who pre-

sent with fulminant disease or advanced and severe renal disease. It was concluded that most patients with microscopic polyangiitis or necrotizing and crescentic glomerulonephritis achieve remission with therapy. Relapses occur in 29% of patients and generally respond to retreatment. Initial treatment with cyclophosphamide and corticosteroids rather than corticosteroids alone results in a lower frequency of relapse. Even patients who require dialysis at presentation may benefit from treatment, however, patients who are not treated until the disease process is life-threatening may die before induction therapy is complete, indicating the continued need for early diagnosis and therapy.

**Key Words:** Vasculitis, anti-neutrophil cytoplasmic autoantibodies

Although the short-term prognosis of patients with small vessel vasculitis has improved over the last 15 to 20 yr (1), long-term preservation of renal function remains a challenge. Considering the inherent danger of available therapeutic options, reliably inducing and maintaining remission, predicting relapses, and adjusting therapy in resistant patients is of utmost importance. These issues are even more difficult in the setting of progressive loss of renal function after a period of stabilization with treatment. Does this constitute a relapse of vasculitis, or is it an inevitable process caused by scarring and fibrosis of the initial inflammatory response? If it is indeed a recurrence of the vasculitic process, what is the risk/benefit ratio of further aggressive treatment?

By using multivariate analysis, we have demonstrated that the strongest predictor of renal survival in patients with antineutrophil cytoplasmic autoantibodies (ANCA)-associated microscopic polyangiitis (MPA) and necrotizing crescentic glomerulonephritis (NCGN) was the entry serum creatinine value (2). Other variables, including age, pulmonary symptoms at disease onset, and ANCA antigen-specificity, were not predictors of outcome. When controlling for entry serum creatinine value, arterial sclerosis on renal biopsy, but not the activity or chronicity of the glomerular injury, was also a predictor of outcome.

In this study, we sought to determine the incidence of complete remission and treatment resistance, and the character and frequency of relapse in patients with MPA and NCGN. We defined specific criteria for remission, resistance, and relapse, and then prospectively applied these criteria to a well-characterized population inception cohort of 107 patients with ANCA-associated MPA and NCGN. Patients with any

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evidence for ANCA-associated granulomatous inflammation (*i.e.*, Wegener's granulomatosis) were excluded from this analysis. Thus, only patients with ANCA-associated MPA and NCGN as defined by the Chapel Hill vasculitis nomenclature (3) form the basis of this evaluation.

## METHODS

### Criteria for Treatment Response

**Remission.** Stabilization or improvement of renal function (as measured by serum creatinine concentration), resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity.

**Remission on Therapy.** The achievement of remission while still receiving immunosuppressive medication or corticosteroids given at a dose greater than 7.5 mg per day of prednisone or its equivalent.

**Treatment Resistance.** (1) Progressive decline in renal function with the persistence of an active urine sediment; or (2) persistence or new appearance of any extrarenal manifestation of vasculitis despite immunosuppressive therapy.

**Relapse.** Occurrence of at least one of the following: (1) rapid rise in serum creatinine concentration accompanied by an active urine sediment; (2) a renal biopsy demonstrating active necrosis or crescent formation; (3) hemoptysis, pulmonary hemorrhage, or new or expanding nodules without evidence for infection; (4) active vasculitis of the respiratory or gastrointestinal tracts as demonstrated by endoscopy with biopsy; (5) iritis or uveitis; (6) new mononeuritis multiplex; or (7) necrotizing vasculitis identified by biopsy in any tissue.

### Patient Population: Serology, Pathology, and Clinical Features

All patients with ANCA-associated MPA and NCGN in this study are followed by members of the Glomerular Disease Collaborative Network. The Glomerular Disease Collaborative Network is a group of 150 nephrologists from 40 private community offices and 3 medical schools, primarily located in North Carolina and throughout the southeastern United States.

A positive ANCA was defined as a cytoplasmic ANCA (C-ANCA) or perinuclear ANCA (P-ANCA) staining pattern on ethanol-fixed human neutrophils, as determined by indirect immunofluorescence microscopy (4). All P-ANCA were further characterized as myeloperoxidase-specific by ELISA (4). C-ANCA were determined to be specific to proteinase 3 in 87% of test samples, by use of an anti-PR3 ELISA Kit (Progen Biotechnik GmbH, Heidelberg, Germany).

Renal biopsies were obtained on all patients at the time of diagnosis and serve as the entry point for the prospective study. All renal biopsy specimens showed a pauci-immune NCGN with less than 2+ immune deposits by direct immunofluorescence microscopy (on a scale of 1 to 4+). Each renal biopsy specimen was scored on the degree of glomerular necrosis (0 to 4), glomerular crescents (0 to 4), glomerular sclerosis (0 to 4), interstitial fibrosis (0 to 4), tubular atrophy/injury (0 to 4) and arterial sclerosis (0 to 4). An activity index (0 to 8) was defined as the sum of the scores for glomerular necrosis and glomerular crescents. The chronicity index (0 to 12) was defined as the sum of the scores for glomerular sclerosis, interstitial fibrosis, and tubular atrophy. If patients had more than one renal biopsy during the course of their follow-up, only the first biopsy was used in the

analysis of prognostic factors. All renal biopsy specimens and ANCA assays were determined by a single nephropathologist (Dr. J.C. Jennette).

Extra-renal manifestations of ANCA-associated vasculitis were frequently observed. Pulmonary involvement was defined by the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, or radiographic proof of infiltrates in the absence of evidence for an infectious etiology. Upper respiratory tract involvement was defined by clinical or radiographic evidence of sinusitis, the presence of ulcers of the nasal passages, with or without epistaxis, or otitis media. Patients with upper respiratory tract involvement were not considered to have Wegener's granulomatosis if there was no evidence of invasive bony disease or granulomatous inflammation. Involvement of the joints was defined by arthritis. Arthralgias and myalgias were common, but were not considered as manifestation of systemic vasculitis. Skin vasculitis was inferred when a typical purpuric rash with or without ulceration was present. Five patients had biopsy proof of leukocytoclastic angitis in the skin. Gastrointestinal involvement included abdominal pain and/or gastrointestinal bleeding not believed to be secondary to corticosteroid therapy. Neurological involvement included seizures, or multifocal neural deficit (mononeuritis multiplex).

Patients were excluded if they were found to have necrotizing granulomatous inflammation on respiratory tract or renal biopsy. These patients were diagnosed with Wegener's granulomatosis on the basis of the Chapel Hill consensus conference nomenclature for systemic vasculitis (3). Patients with evidence of nodular or cavitary lesions on chest roentgenogram were also excluded, as well as one patient with significant facial bone erosion because of a mass lesion in the sinuses and pansinusitis.

Patients were followed prospectively from the time of their diagnosis. Review of past medical records was used to determine onset of symptoms and laboratory values before diagnosis of ANCA-associated disease. Patients were followed until: (1) there was irreversible loss of renal function, requiring dialysis or transplantation (if before dialysis); or (2) death. Patients not reaching an end point were followed until the date of their most recent office visit or hospital discharge. Overall, 88 (82%) patients were followed until the occurrence of an end point or to within 6 months of the end of the study. One patient was lost to follow-up after 12 months. The remaining 18 patients were stable and seen by their physician within 12 months of the end of the study.

This study was approved by the University of North Carolina Committee on the Protection of Human Rights.

### Treatment Protocols

In this inception cohort trial, patients were treated with three different protocols, depending on the decision of the treating physician. Patients were included in this trial on the basis of "intention" to treat with one of the following modalities. The treatment protocols have been previously described (5). In brief, induction therapy consisted of pulse methylprednisolone given at a dose of approximately 7 mg/kg on each of 3 consecutive days. Prednisone was then continued at a dose of 1 mg/kg for the first 4 wk, followed by a tapering schedule over the next months. All patients received corticosteroids. In addition to corticosteroids, patients receiving oral cyclophosphamide were treated for 6 to 12 months, with an initial dose of 2 mg/kg. This dose was manipulated in all patients, depending on the total leukocyte count. The third treatment modality was based on six monthly intravenous

cyclophosphamide doses given at an initial dose of 0.5 g/m<sup>2</sup>. This dose was increased to a maximum of 1.0 g/m<sup>2</sup> and adjusted according to the 2-week leukocyte nadir. Plasma exchange was added in four patients with massive pulmonary hemorrhage.

Of the 107 patients eligible for this cohort study, ten patients (8%) received no treatment because of death before treatment (*N* = 1), because the treating physician considered the patient to have unrecoverable renal disease (*N* = 4), because of advanced age (*N* = 1, age 92), or for unexplained reasons (*N* = 3). Only one patient was lost to follow-up.

## Statistical Methods

Comparisons between groups were done by Fisher's exact test and continuity adjusted chi-square test for categorical variables, and Wilcoxon rank-sum tests for continuous variables.

The Cox proportional hazards model was used to estimate the effect of therapy with cyclophosphamide versus corticosteroids on the risk of relapse. The start date for entry into the study was the date of renal biopsy. An end point was defined as relapse. Patients were censored at their last follow-up date if they did not experience a relapse, if they died secondary to causes unrelated to relapse, or reached dialysis without signs of relapse. Other potential independent prognostic variables were controlled for in assessing the effect of therapy, including duration of treatment ( $\leq 6$  months versus  $> 6$  months), peak entry serum creatinine value (as natural log), presence of arterial sclerosis on renal biopsy, age ( $< 25$  yr of age versus 25 to 70 yr of age versus  $> 70$  yr of age), ANCA specificity (P-ANCA versus C-ANCA), and disease category (MPA versus NCGN). Smaller divisions of age groups were not possible because of the sample size.

## RESULTS

Of the 107 patients eligible for this cohort study, ten patients received no treatment. Of these patients, six with severe renal impairment required dialysis at or within 1 month of presentation, three died within 3 wk of presentation, and one went into remission with residual chronic renal insufficiency after a follow-up period of 16 months.

Of the 97 patients who received treatment, there were 53 men and 44 women. The average age was 57.6  $\pm$  16.7 yr, with a median of 61 yr and a range of 2 to 81 yr. Patients were followed for a mean of 2.7  $\pm$  2.4 yr, with a range of 3 days to 12 yr. Of these patients, 61 had a P-ANCA pattern and 36 had a C-ANCA pattern. This predominance of P-ANCA patients would be expected in a population in which patients with Wegener's granulomatosis are excluded.

Sixty-five patients had MPA, and 32 had NCGN. The distribution of presenting organ system involvement is noted in Table 1. Twenty-five patients (26%) received corticosteroids alone, whereas 72 (74%) received intravenous or oral cyclophosphamide in addition to corticosteroids.

Using the definition of treatment as intention to treat, 75 of 97 patients (77%) responded and went into complete remission. At the time that this study was censored (April 1994), 14 of these patients were in remission on therapy (Figure 1). Of the 75 responders,

TABLE 1. Organ involvement<sup>a</sup>

Organ System Involvement	Number of Patients	% of Patients	MPA	NCGN
Total Number of Patients	107		69	38
Renal	107	100	69	38
Pulmonary	38	36	38	0
Upper Respiratory Tract	14	13	14	0
Musculoskeletal	10	9	10	0
Neurologic	9	8	9	0
Gastrointestinal	6	6	6	0
Cutaneous	13	12	13	0
Ocular	2	2	2	0

<sup>a</sup> MPA, microscopic polyangiitis; NCGN, necrotizing crescentic glomerulonephritis.

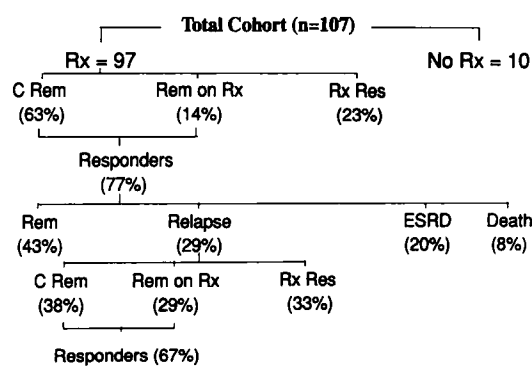


Figure 1. The response to treatment and outcome of the 107 eligible patients with MPA and NCGN. Rx, treatment; C Rem, complete remission; Rem on Rx, remission on therapy; Rx Res, treatment resistant; ESRD, end stage renal disease.

32 patients (43%) remained in long-term remission, for a mean follow-up of 44  $\pm$  29 months (median, 37.8; range, 2.9 to 105). There was no difference in the rate of response between patients with MPA when compared with NCGN alone (77% versus 78%) (Table 2).

Fifteen patients (20%) progressed to ESRD without signs of active renal disease and without any other evidence of relapse of their disease. ESRD occurred in these individuals after a mean of 21.4  $\pm$  22.8 months (median, 12.2; range, 0 to 79). There were no differences in their mean scores for any of the pathological indices when compared with patients who did not progress to ESRD. Six patients died during the period of follow-up. Two patients died from septicemia, presumably as a consequence of the immunosuppressive therapy. One of these patients died of polymicrobial sepsis caused by a vasculitic lesion in the gastrointestinal tract. Four patients died from causes presumed to be unrelated to systemic vasculitis, including carcinoma (*N* = 2) and myocardial infarction (*N* = 2). These four patients were 2, 60, 67, and 76 yr old.

## Relapse

Twenty-two patients (29% of responders) suffered a relapse in a mean of 15.2  $\pm$  18.8 months (median, 9.8;

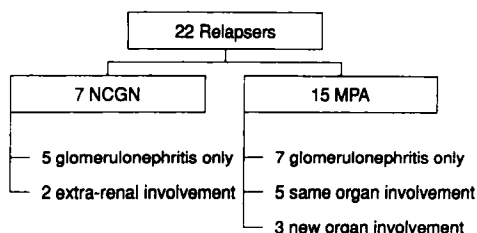
**TABLE 2. Response to treatment, by diagnostic group**

	Patients Treated (N)	Respondents (%)	Resistant (%)
MPA	65	77	23
NCGN	32	78	22
Total	97	77	23

range, 0 to 84.3; 80% < 18 months) after completion of their initial treatment. Of these 22 patients, 16 (73%) had MPA whereas six (27%) had NCGN alone. C-ANCA were found in seven patients, and P-ANCA in 15 patients. Seven patients were treated with corticosteroids alone and 15 were treated with cyclophosphamide.

Among the 22 patients who relapsed, seven had initially presented with NCGN alone. Of these seven, five relapsed with glomerulonephritis only, one relapsed with pericardial involvement, and one with skin involvement. Of the 15 patients who presented initially with evidence of extrarenal vasculitis, seven had recurrent glomerulonephritis only. Five of the remaining eight patients experienced a relapse with involvement of the same extrarenal organ or organ systems as on initial presentation, and three experienced a relapse in different organ systems (Figure 2). Irrespective of the site of relapse, many patients reported as their first symptom of recurrent disease the return of the migratory polyarthropathy that characterized the initial onset of their disease.

Of the 22 patients who relapsed, all but one were retreated (Figure 1), four with corticosteroids only, 16 with cyclophosphamide (seven orally and nine intravenously), and one with azathioprine. Fourteen patients (66.6%; ten treated with cyclophosphamide, three with corticosteroids, and one with azathioprine) had a response to their second course of therapy, including nine who went into remission for a mean of  $36.6 \pm 24.3$  months (median, 29.7 months; range, 3.5



**Figure 2. The distribution of organ involvement at the time of relapse.** Among the seven patients who presented initially with NCGN alone, five relapsed with glomerulonephritis only and two with extrarenal involvement. Of the 15 patients who presented initially with MPA, seven relapsed with glomerulonephritis only, five had recurrent disease in the same organ systems as on initial presentation, and three had involvement of new organ systems.

**TABLE 3. Outcome of respondents, by diagnostic group**

	Patients Treated (N)	Remission (%)	Relapse (%)	ESRD (%)	Death (%)
MPA	50	38	32	24	6
NCGN	25	52	24	12	12
Total	75	43	29	20	8

to 54.8), three had a second relapse within a mean of 10 months (range, 1.5 to 23), one progressed to ESRD in 23 months, and one died. The percent response to treatment is slightly lower at the time of relapse than at initial presentation (66.6% versus 77.3%,  $P = 0.332$ ), but there is no significant difference in the distribution of outcomes. Only one patient had three relapses before reaching an end point.

### Comparison of Treatment Modalities

In a previous analysis based on the same cohort of patients, we found that treatment with cyclophosphamide was beneficial over the use of corticosteroids alone for patient survival ( $P = 0.012$ ) (2). In the study presented here, we evaluated whether the choice of cyclophosphamide or corticosteroid therapy affects the risk of relapse.

To assess the effect of treatment modality on remission and relapse, we compared the outcome distribution of the corticosteroid- and cyclophosphamide-treated groups. There was no statistical difference in the rate of response to treatment (Table 2) nor in the distribution of the various outcomes among the two disease categories (Table 3) ( $P = 0.413$ ). Therefore, these two groups were combined for the study of the effect of treatment modality on remission and relapse. Similarly, there was no statistical difference in the rate of remission or relapse between the intravenous- and oral-cyclophosphamide treated groups, therefore, these two groups were also combined.

There was a significant difference in the remission rate between the corticosteroid-treated patients and the cyclophosphamide-treated patients (56% versus 84.7%,  $P = 0.003$ ). Among the 75 patients who responded to their initial treatment, cyclophosphamide-treated patients were approximately half as likely to suffer a relapse as the corticosteroid-treated patients (risk ratio, 0.50; 95% CI, [0.20, 1.1]), this difference did not reach statistical significance ( $P = 0.09$ ).

Because our study was an inception-cohort design rather than a randomized trial, differences in response to treatment and outcome among the treatment groups could be the result of a selection bias, such as the reluctance of some physicians to give an alkylating agent to the elderly or very sick patient. To address this possibility, we have analyzed the data with multivariate analysis, controlling for age, peak serum creatinine level, duration of therapy, and pres-

ence of arterial sclerosis in a multivariate model. When controlling for these variables, the effect of treatment modality on the risk of relapse was strengthened. Cyclophosphamide-treated patients had approximately three times less risk of experiencing a relapse than corticosteroid-treated patients (risk ratio, 0.31; 95% CI, [0.12, 0.84]). This difference was statistically significant with a *P* value that equaled 0.026. None of the covariates—including peak serum creatinine concentration—were prognostic indicators of relapse, but each had a confounding effect on the relationship of treatment modality to relapse. ANCA-specificity and disease category were not kept in the model because they were not predictive of outcome and did not confound the effect of treatment modality on relapse.

### Treatment Resistance

A total of 22 patients were considered treatment resistant. Table 4 depicts some of the clinical and pathologic features of the resistant and responsive groups. Treatment-resistant patients were on average slightly older ( $61.3 \pm 16.4$  versus  $56.5 \pm 16.7$ , medians 67 versus 61) and had a somewhat higher average peak serum creatinine level than that of responders ( $6.9 \pm 4.3$ ; range, 1.5 to 16 versus  $5.2 \pm 3.6$ ; range, 0.8 to 21.6). The difference in mean serum creatinine value approached but did not reach statistical difference (*P* = 0.07). In addition, there was no difference in the pathology scores for activity and chronicity between the two groups nor was there a difference in the proportion of each disease group.

Of these 22 treatment-resistant patients, 11 were treated with corticosteroids alone and 11 with cyclophosphamide (two orally and nine intravenously). Six patients succumbed to fulminant disease soon after presentation and during the induction phase of therapy (Figure 3). Of the remaining 16 patients, 11 patients presented with advanced renal disease requiring dialysis at the time of or within 1 month of presentation. Of the remaining five patients, two patients received a shortened course of therapy because of complications of therapy (one patient with cholestatic jaundice secondary to cyclophosphamide, one patient with sepsis). The remaining three patients

TABLE 4. Clinical and pathological features of resistant and responsive groups

Feature	Treatment Resistant	Treatment Responsive
<i>N</i>	22	75
Age (Mean $\pm$ SD)	$61.3 \pm 16.4$	$56.5 \pm 16.7$
Serum Creatinine (mg/dL) (Mean $\pm$ SD)	$6.9 \pm 4.3$	$5.2 \pm 3.6$
Chronicity (Mean $\pm$ SD)	$5.2 \pm 2.1$	$4.7 \pm 2.5$
Activity (Mean $\pm$ SD)	$3.6 \pm 1.8$	$3.7 \pm 2$
MPA	68%	67%
NCGN	32%	33%

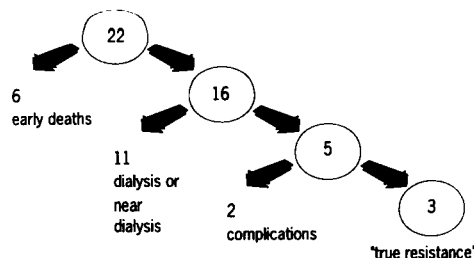


Figure 3. Treatment resistance. Of the 22 treatment-resistant patients, six succumbed to fulminant disease during induction therapy, 11 patients presented with advanced renal disease requiring dialysis, and two received a shortened course of treatment secondary to complications of therapy. The remaining three patients progressed to ESRD despite a relatively young age and early institution of therapy.

progressed inexorably to ESRD despite their relatively young ages ( $47 \pm 11.5$ ; range, 38 to 60) and early institution of therapy (mean creatinine value,  $3.4 \pm 0.5$ ; range, 3 to 4; mean chronicity index,  $3.3 \pm 2.4$ ; range, 1.5 to 6). These three patients represent a group of "truly resistant" patients, representing 3% of our treated cohort.

### Treatment Response of Patients on Dialysis

We were interested in evaluating the response to treatment and outcome of patients who present initially with severe renal damage requiring dialysis within 30 days of diagnosis and biopsy, paying particular attention to those who improve transiently with therapy but subsequently progress to ESRD and dialysis. The purpose of this analysis was to provide an assessment of the risks versus the potential benefits of therapy for patients presenting at or near ESRD.

A total of 23 patients required dialysis at the time of their initial presentation, and their average creatinine concentration was  $10.9 \pm 4$  (median, 10.4; range, 3.2 to 21.6). Of these 23 patients, 17 received treatment: 13 with cyclophosphamide (six orally and seven intravenously) and four with corticosteroids alone (Figure 4). Nine patients (53%) responded and eight (47%)

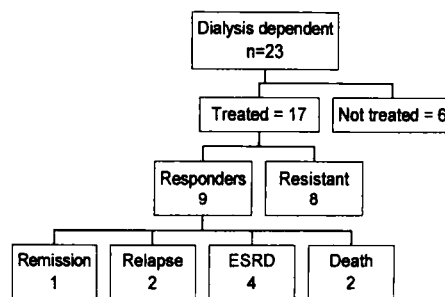


Figure 4. The response to treatment and outcome of patients on dialysis. Of the 17 patients who received treatment, nine achieved a remission. Of these, one remained in long-term remission, two had a relapse, four progressed to ESRD without evidence of a relapse, and two patients died.

were treatment resistant. There was no significant difference in the ages (median ages 69 versus 73.5), serum creatinine concentration ( $11.3 \pm 4.8$  versus  $10.4 \pm 4.6$ ), or chronicity or activity indices (chronicity,  $5 \pm 2$  versus  $5.5 \pm 2.2$ ; activity,  $6.2 \pm 1.2$  versus  $4.2 \pm 1.9$ ) between the respondent and resistant groups.

The nine patients who responded to therapy came off dialysis an average of 6 weeks after the beginning of treatment (range, 1 to 10 wk). Of these nine patients, one remained in remission over a 7-month follow-up, two relapsed in a mean of 17 months after the end of therapy ( $22.61 \pm 11.2$  months from presentation;  $17.2 \pm 9.2$  months from end of treatment), two patients died (one of a myocardial infarction and one of sepsis), and four progressed to ESRD in a mean of  $23.8 \pm 13.4$  months (median 24.2 months) from presentation.

## DISCUSSION

In our patients with ANCA-associated MPA and NCGN, the overall risk of relapse after responding to the initial treatment was 29%, with an average follow-up of 44 months (range, 2.9 to 105 months). Eighty percent of relapses occurred within the first 18 months after the end of therapy, although a few continued to occur with prolonged follow-up. Although the number of patients was small, it appears that patients presenting with NCGN alone also have renal-limited disease on relapse. Similarly, patients with MPA tend to relapse in the same organ systems as on initial presentation. A new organ involvement occurred in only 23% (5 of 22) of patients. Fortunately, response to treatment of a relapse (66%) is similar to the response to treatment of the initial disease (77%). Retreatment is an important and beneficial option.

There are a few published studies that specifically address the issue of relapse in patients with Wegener's granulomatosis (6–8) or in vasculitis in general, without specific attention to MPA and NCGN (9). Two retrospective studies specifically provide long-term follow-up and relapse data in patients with MPA and NCGN (10,11). Significant differences in treatment protocols make it difficult to extrapolate these results to our own. In the report by Gordon *et al.* (11), the rate of relapse reported for MPA (25.4%) is comparable to ours. Although these authors did not observe a clustering of relapse within the first years after treatment, they report a median time to relapse of 24 months. Our studies differ in that our patients did not receive substantial immunosuppression after 6 months, whereas the patients in the study by Gordon *et al.* received a prolonged regimen of maintenance therapy with corticosteroids. Both studies suggest the need for close follow-up for at least 2 yr after the end of treatment.

In our cohort, patients were treated according to the same treatment guidelines for relapse as for the initial disease. The concern is raised about exposing relaps-

ing patients to repetitive cycles of cytotoxic drugs with the risk of infection and malignancies (12–15). The best mode of therapy for relapse remains to be determined. Several "alternative" therapeutic options for vasculitis have been suggested but most reports are limited to a small number of patients with Wegener's granulomatosis and almost none of them specifically address the treatment of relapsing disease. Such options include cyclosporin A (16,17), azathioprine (widely used in Europe for postinduction treatment) (1,6,10,11,18), methotrexate (19), and intravenous pooled immune globulin (20,21).

Our study has limitations in comparing treatment modalities because patients were not randomized to one or the other treatment group. We addressed the issue of bias by comparing the two treatment groups after controlling for independent prognostic variables such as age, peak serum creatinine concentration, and duration of treatment. Our raw data, as well as the results of the multivariate modeling, point to a beneficial effect of cyclophosphamide over corticosteroids alone on the risk of relapse. Similarly, treatment with cyclophosphamide has a beneficial effect on patient survival when compared with treatment with corticosteroids alone (2).

It was our impression at the beginning of this study that patients who did not respond to treatment failed to do so because of late presentation, with severe "unrecoverable" damage to the renal parenchyma having already occurred. Our data do not support the concept that resistance to treatment can be reliably predicted on the basis of age, serum creatinine concentration, or pathological activity or chronicity scoring (as was suggested by Dupre-Goudable (22)).

Seventy-seven percent (17 of 22) of treatment resistance occurred in patients who presented with fulminant disease or advanced and severe renal disease. These results emphasize the importance of prompt diagnosis and institution of therapy. Complications of therapy accounted for only a small percentage (9%) of treatment failures. We have however identified a subgroup of patients (3% of our initial cohort) who resisted therapy despite having what intuitively should have been a good prognosis because of a relatively young age, with moderate impairment in renal function and early institution of treatment.

Considering the difficulties and risks involved with the current immunosuppressive treatment of ANCA-associated vasculitis, it is interesting to assess the prognosis of patients presenting evidence of severe renal insufficiency requiring dialysis. Although some of these patients were known to respond to treatment sufficiently to come off dialysis (6), it was thought that this improvement was only transient, and that ESRD was an inexorable result. In a separate study using multivariate analysis, we have shown that the entry serum creatinine concentration is the single best predictor of outcome in this same population with a mean follow-up of 24 months (2). It therefore becomes important to determine whether there is a threshold of

renal damage beyond which the chances of recovery or the benefits of therapy do not justify the risks. By analyzing the response to treatment and outcome of 23 patients who presented with disease severe enough to require dialysis, our data suggest that dialysis requirement at presentation does not necessarily indicate treatment resistance or a bad prognosis (9 of 17 patients who received treatment were able to come off dialysis). Even for the patients who eventually reached ESRD, treatment provided a median of 2 dialysis-free yr. The majority of patients (78%) who responded to therapy and came off dialysis did so within 2 months after the initiation of treatment, and all did within 3 months. We have been unable, therefore, to determine a threshold beyond which treatment would not be recommended. Although these data are based only on a small number of patients, they strongly argue against withholding treatment from patients who require dialysis at the time of presentation. One reasonable approach to the dialysis dependent patient is to initiate therapy as promptly as possible, and discontinue it if no improvement is achieved after 2 months.

In conclusion, our data demonstrate that: (1) the majority of patients respond to treatment with corticosteroids alone or in combination with cyclophosphamide; (2) relapse occurs in about one third of patients who achieve a remission, usually within 18 months after the end of treatment; (3) treatment with cyclophosphamide decreases the risk of relapse when compared with corticosteroids alone; and (4) initial dialysis requirement should not be a contraindication for treatment, even though severe renal failure at the time treatment is begun is a predictor of poor long-term outcome (2).

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