Treatment Response and Relapse in Antineutrophil Cytoplasmic Autoantibody-Associated Microscopic Polyangiitis and Glomerulonephritis

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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 ± 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 presented 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...
Treatment Response in ANCA Vasculitis

Evidence for ANCA-associated granulomatous inflammation (i.e., Wegner'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 angiitis 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

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cyclophosphamide doses given at an initial dose of 0.5 g/m². This dose was increased to a maximum of 1.0 g/m² 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 without signs of relapse, or reached dialysis due to reasons unrelated to systemic vasculitis. Patients were censored at their last follow-up date if they did not experience a relapse, if they died without signs of relapse, or reached dialysis due to reasons unrelated to systemic vasculitis.

Other potential independent prognostic variables were controlled for in assessing the effect of therapy, including duration of treatment (< 6 months versus > 6 months), presence of arterial sclerosis on renal biopsy, 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 ± 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 ± 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, 32 patients (43%) remained in long-term remission, for a mean follow-up of 44 ± 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 ± 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 ± 18.8 months (median, 9.8;
TABLE 2. Response to treatment, by diagnostic group

<table>
<thead>
<tr>
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<th>Patients Treated (N)</th>
<th>Respondents (%)</th>
<th>Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>65</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>NCGN</td>
<td>32</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>77</td>
<td>23</td>
</tr>
</tbody>
</table>

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 \( (56\% \text{ versus } 84.7\%, P = 0.003) \). 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 \( (\text{risk ratio}, 0.50; 95\% \text{ CI}, [0.20, 1.1]) \), 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 ± 16.4 versus 56.5 ± 16.7, medians 67 versus 61) and had a somewhat higher average peak serum creatinine level than that of responders (6.9 ± 4.3; range, 1.5 to 16 versus 5.2 ± 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, 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.

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Treatment Resistant</th>
<th>Treatment Responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>75</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>61.3 ± 16.4</td>
<td>56.5 ± 16.7</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL) (Mean ± SD)</td>
<td>6.9 ± 4.3</td>
<td>5.2 ± 3.6</td>
</tr>
<tr>
<td>Chronicity (Mean ± SD)</td>
<td>5.2 ± 2.1</td>
<td>4.7 ± 2.5</td>
</tr>
<tr>
<td>Activity (Mean ± SD)</td>
<td>3.6 ± 1.8</td>
<td>3.7 ± 2</td>
</tr>
<tr>
<td>MPA</td>
<td>68%</td>
<td>67%</td>
</tr>
<tr>
<td>NCGN</td>
<td>32%</td>
<td>33%</td>
</tr>
</tbody>
</table>

progressed inexorably to ESRD despite their relatively young ages (47 ± 11.5; range, 36 to 60) and early institution of therapy (mean creatinine value, 3.4 ± 0.5; range, 3 to 4; mean chronicity index, 3.3 ± 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 ± 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%)
were treatment resistant. There was no significant
difference in the ages (median ages 69 versus 73.5),
serum creatinine concentration (11.3 ± 4.8 versus
10.4 ± 4.6), or chronicity or activity indices (chronic-
ity, 5 ± 2 versus 5.5 ± 2.2; activity, 6.2 ± 1.2 versus
4.2 ± 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 ± 11.2 months from presentation;
17.2 ± 9.2 months from end of treatment), two pa-
tients died (one of a myocardial infarction and one of
sepsis), and four progressed to ESRD in a mean of
23.8 ± 13.4 months (median 24.2 months) from pre-
sentation.

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 fol-
low-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. Al-
though 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, with-
out 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 clus-
tering 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 deter-
mined. 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 op-
tions 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 corticoste-
roids alone on the risk of relapse. Similarly, treatment
with cyclophosphamide has a beneficial effect on pa-
tient 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 hav-
ing already occurred. Our data do not support the
concept that resistance to treatment can be reliably
predicted on the basis of age, serum creatinine con-
centration, or pathological activity or chronicity scor-
ing (as was suggested by Dupre-Goudable (22)).

Seventy-seven percent (17 of 22) of treatment resis-
tance occurred in patients who presented with fulmi-
nant 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 sub-
group of patients (3% of our initial cohort) who re-
sisted therapy despite having what intuitively should
have been a good prognosis because of a relatively
young age, with moderate impairment in renal func-
tion 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 pre-
dictor of outcome in this same population with a mean
follow-up of 24 months (2). It therefore becomes im-
portant 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 months. We have been unable, therefore, to determine if no improvement is achieved after 2 months; (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).

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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