Predictors of Renal Outcomes in Sclerotic Class ANCA GN

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Abstract

Background:

The prognostic value of the ANCA associated glomerulonephritis (ANCA GN) classification has been demonstrated in several cohorts with sclerotic class having the worst renal outcome. Relevant published data on factors predicting outcomes in sclerotic ANCA GN is limited.

Methods:

Sclerotic ANCA GN patients were recruited from 5 centers worldwide for this retrospective cohort study. We describe the clinical characteristics of this cohort and evaluate predictors of one-year GFR and ESRD. Kidney function at 12 months as measured by MDRD eGFR was modeled by simple and multiple linear regression. We used Cox proportional hazards regression modeling to evaluate ESRD-free survival.

Results:

Of the 50 patients, 92% were Caucasian and 60% male with a mean age of 61 years. 72% had renal limited disease and 82% were MPO ANCA positive. Kidney biopsies contained a median of 20 (IQR 15-34) glomeruli with 96% showing moderate to severe interstitial fibrosis. 96% of patients received immunosuppressive drug therapy and 16% received plasmapheresis. Treatment response was achieved in all but one patient. The median (IQR) eGFR at entry was

14.5 (9-19) ml/min/1.73m2. Over a median (IQR) follow up of 33.5 (17-82) months, 26 patients reached ESRD. Ten patients died with six of them occurring within the first year of diagnosis. The hazard of progression to ESRD was significantly higher in those with lower GFR at study entry (p=0.003) and with higher degree of tubular atrophy (p=0.043).

Conclusions:

Renal recovery is rare among sclerotic ANCA GN patients requiring dialysis at entry and 12% of patients died in the first year. Entry GFR and tubular atrophy were significant predictors of GFR at 12 months and renal survival in patients with sclerotic class ANCA GN.

1. Introduction:

The ANCA associated vasculitides (AAV) are systemic necrotizing vasculitides characterized by the presence of circulating anti-neutrophil cytoplasmic antibody (ANCA) in about 90% of patients.[1] AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis and renal limited vasculitis.[2] ANCA-associated glomerulonephritis (ANCA GN) is present more than 50% of AAV patients at diagnosis and about 70-85% of these patients develop renal vasculitis during their disease course.[3] Severe renal dysfunction portends a poor prognosis and causes end stage renal disease (ESRD) or death in 50% of patients at 5 years.[3, 4] Recent advances in therapy have transformed AAV from a fatal disease to one with a relapsing course but substantial treatment related morbidity exists. Data from the European vasculitis study group demonstrates that the mortality is highest in the first year with most of them being attributable to infection.[5] Prognosis is an important issue in renal vasculitis where both the disease and therapies may lead to significant morbidity and mortality.

Several histopathologic studies have demonstrated that the combination of GFR at baseline and renal histology is a better predictor of renal outcome than GFR alone.[6-12] In 2010, an international working group of renal pathologists proposed a new classification for ANCA GN based on glomerular pathology to assess its predictive value for renal survival and

validated it using patient data.[13] The classification system categorized ANCA GN into four classes based on glomerular pathology: focal, crescentic, mixed and sclerotic. Subsequent to this study, a number of validation studies in several cohorts in Europe, Asia and United States confirmed the predictive value of this classification for renal survival in focal and sclerotic class and mixed results in crescentic and mixed class.[14] The sclerotic class ANCA GN had the worst short and long term renal survival. Following treatment, the one and five-year renal survival in these patients is about 50% suggesting that renal function can be stabilized with treatment in a significant number of patients. There is lack of data on prognostic markers to identify patients who progress to ESRD where immunosuppression is likely to cause more harm than benefits. This study aims to determine prognostic markers of renal outcome among patients with sclerotic class ANCA GN.

2. Methods:

The study patients were recruited from five centers worldwide (United States, the United Kingdom, the Czech Republic, Ireland and China). Patients were eligible for study entry if they had ANCA-associated GN clinically as well as biopsy-proven sclerotic class ANCA GN, defined as >50% of glomeruli on biopsy sample demonstrating global sclerosis. Biochemical, clinical measurements and details of immunosuppressive therapy were recorded with time origin being the time of kidney biopsy. The number of normal glomeruli, glomeruli with cellular crescents and fibrocellular crescents were recorded for each biopsy by review of paper reports and slides. The degree of interstitial fibrosis and tubular atrophy was graded mild (<25%), moderate (25 to 50%) or severe (>50%) depending on extent of involvement. Patients with missing data regarding diagnosis of ESRD, estimated glomerular filtration rate (eGFR), both at baseline and at 12 months, were excluded from analysis. Treatment response was defined clinically by stabilization or improvement of serum creatinine with resolution of hematuria and absence of signs of extra-renal vasculitis. Relapse was defined by biopsy proven pauci-immune GN or an increase in

vasculitis activity requiring an increase in immunosuppressive drug therapy. The study was approved by Institutional review board at each center. Notably, because there is no standardized treatment guidelines for sclerotic class ANCA vasculitis, patients observed in this study underwent a number of different immunosuppression regimens as will be explained in detail below. The study outcomes were 12-month eGFR based on the equation derived by Levey and colleagues based on the Modification of Diet in Renal Disease (MDRD) Study and ESRD defined as need for initiation of renal replacement therapy in the form of dialysis or transplant.[15] Estimated GFR at 12 months was modeled as a function of various predictors using both simple and multiple linear regression. The hazard of ESRD was modeled using Cox proportional hazards regression in both univariable and multivariable analyses. The Breslow method was used for ties. The outcome of ESRD-free survival was further demonstrated with Kaplan-Meier survival curves. The degree of tubular atrophy and interstitial fibrosis were categorized as mild, moderate, or severe on biopsy. All analyses were run using Stata Version 15 (Stata Corporation, College Station, TX).

3. Results:

Of the fifty patients who met the inclusion criteria, 92% were Caucasian and 60% were male with a median overall age at biopsy of 63.5 (IQR 50-73) years. Eight patients (16%) were positive for PR3 and forty-one (82%) were positive for MPO. The remaining patient was ANCA negative by serolgies but with a biopsy showing pauci-immune vasculitis with evidence of sclerosis. Thirty-six patients (72%) had renal limited AAV and the remaining patients had evidence of extra-renal disease. The median eGFR at entry was 14.5 (IQR 9-19) ml/min/1.73m^2. Baseline characteristics can be found in Table 1.

Kidney biopsies obtained a median of 20 (IQR 15-34) glomeruli, of which 23 specimens (46%) had some evidence of fibrocellular crescents, while 28 (56%) had some evidence of fibrous crescent formation. Only two biopsies had less than ten glomeruli for analysis. The

median percent sclerosed glomeruli in samples was 67 (IQR 59-75). In total, 48 biopsy samples (96%) showed moderate to severe interstitial fibrosis (IF). Only twenty patients (40%) had any normal-appearing glomeruli on biopsy, and of these, over half (12 patients) had only 1-2 normal glomeruli visualized. 32 specimens (64%) had at least one cellular crescent, while 11 (22%) had 3 or more. Out of thirty-two patients with evidence of tubular atrophy on biopsy, two were classified as mild and thirteen showed moderate atrophy, while the majority (17) demonstrated severe atrophy.

A total of forty-eight patients (96%) were treated with immunosuppressive medications. Eight patients also received plasmapheresis. Thirty-five patients (70%) received pulse intravenous (IV) methylprednisolone, while thirty-two (64%) received cyclophosphamide. Of the thirty-two patients treated with cyclophosphamide, twenty-four (75%) received IV cyclophosphamide while the remaining eight received the oral formulation. Eleven (22%) patients received IV rituximab and four patients received both cyclophosphamide and rituximab (8%) (Table1). Of the 48 patients treated with immunosuppressive therapy with or without plasmapheresis, one patient never achieved treatment response despite treatment with cyclophosphamide and rituximab. Of the two patients who did not receive any immunosuppression, both had renal-limited disease and progressed to ESRD.

Outcomes were observed in the clinical setting with follow-up times varying by center, but on average 2-3 months between visits. Overall, treatment response was achieved in nearly all patients undergoing treatment (n=47/48, 98%), which occurred in the first 4-6 months of follow-up. Out of the forty-eight who received immunosuppression, thirty-four patients received maintenance immunosuppression. Of those patients who achieved initial treatment response, nine (18.3%) experienced relapse, five of which involved the kidney. Ten patients died during follow up with 6 of them in the first year of diagnosis. Of the six early deaths, three were infection related, one patient died after complications of femoral neck fracture and the cause of death was unknown in two patients. One of the six patients was HD-dependent at study entry.

For our analysis, kidney function at 12 months was first modeled by simple linear regression, excluding those 6 patients who died within the first year from analysis (Supplemental Table 1). In univariable analysis, entry eGFR was positively associated with eGFR at 12 months (β=1.16 mL/min/1.73m^2; 95% CI: 0.816, 1.51). The degree of tubular atrophy was also statistically significantly associated with 12-month GFR (β=-10.5 mL/min/1.73m^2; 95% CI: -18.4, -2.67). With regard to treatment, there was a statistically significant higher 12-month eGFR in patients who received rituximab (β=14.0 mL/min/1.73m^2; 95% CI 6.58, 21.5), while the use of cyclophosphamide was statistically significantly associated with a *lower* GFR at 12 months (β= -11.1 mL/min/1.73m^2; 95% CI -18.6, -3.63). Age and degree of interstitial fibrosis were not statistically significantly associated with eGFR at 12 months, though a higher degree of interstitial fibrosis approached clinical significance with a decline in GFR. Further, there was no statistically significant association between 12-month eGFR and gender, ANCA type, or other pathologic features (percentage of normal glomeruli, percentage of cellular crescents). In our multivariable model, further adjusted for use of rituximab and cyclophosphamide, both entry GFR and degree of tubular atrophy remained statistical significant (r^2=0.722; Table 2).

Among the thirty-eight patients *not* requiring hemodialysis (HD) at study entry, fifteen went on to develop ESRD (39.5%) compared to eleven out of the twelve patients on HD at study entry (91.7%) (Supplemental Figure 1). All thirty-eight patients were treated with immunosuppression and even those who eventually progressed to ESRD showed some initial treatment response. In total, ten of the twelve patients who were HD dependent at study entry received at least some immunosuppression, of which only one had treatment response. The incidence rate of ESRD for those who were on HD at the time of diagnosis was 40.7/100 person-months (95% CI: 22.7, 73.6). In comparison, for the 38 patients who were not HD-dependent at the start of diagnosis, the incidence rate of ESRD was 5.88/100 person-months (95% CI: 3.55, 9.76)

ESRD-free, or renal, survival was modeled with Cox proportional hazards regression (Tables 3, Supplemental Table 2). In univariable analysis, there was a statistically significantly increased hazard of progressing to ESRD with lower eGFR at study entry (1.11, 95% CI 1.04, 1.19). Similarly, dialysis-dependence at study entry was also associated with an increased hazard of ESRD (HR=11.1, 95% CI: 4.04, 30.7). A higher degree of tubular atrophy was associated with progression to ESRD as well (HR=2.69, 95% CI: 1.03, 7.01). In a multivariable model including both entry GFR and degree of tubular atrophy, entry-GFR remained statistically significantly associated, with a lower hazard of ESRD with higher GFR, while the risk of ESRD with increasing tubular atrophy was no longer statistically significant. Tubular atrophy was classified as mild, moderate, or severe and modeled accordingly. Renal survival was visually depicted using Kaplan-Meier graphs showing the differential progression to ESRD by these variables (Figures 1-2, Supplemental Figure 2). For the purposes of the Kaplan-Meier graphs, entry GFR was broken up into eGFR <15, 15-30, and >30 mL/min/1.73m^2.

4. Discussion:

We report the results of the largest series of sclerotic class ANCA GN patients that aimed to ascertain predictors of renal outcome. In this study, baseline GFR and tubular atrophy are predictors of both one-year GFR and overall renal survival. The study demonstrates that renal recovery is very rare among patients who are dialysis dependent at entry.

This study comprised on predominantly MPO ANCA positive patients. This might directly be related to the inclusion of only sclerotic class ANCA GN in this study and reflects high prevalence of chronic lesions in MPO ANCA patients seen in prior studies.[9, 16] Entry GFR has been shown to be an independent predictor of renal outcome in multiple cohorts [4, 8, 9, 17-19] and remains the best predictor in this study comprised of sclerotic class ANCA GN. In fact,

the correlation of entry GFR with long term renal outcome is so strong that the prognostic significance of ANCA GN classification disappears when adjusted for entry GFR.[19]

The prognostic value of the ANCA GN classification was strengthened by adding the percent normal glomeruli in the crescentic and mixed ANCA GN [20] or by adding percent crescent in mixed class.[19]. Among the histologic predictors of renal outcome, percent normal glomeruli has been demonstrated to predict renal function in previous studies. A correlation between percentage normal glomeruli and renal function has been demonstrated in previous studies.[6-9, 11, 12, 19]. In patients with crescentic and mixed type ANCA GN, the presence of >25% normal glomeruli was predictive of improved GFR. [20] The findings in this study are in contrast and this may be related to the overall chronicity score seen in our cohort.

Cellular crescents have been shown to respond to immunosuppressive therapy and subsequent improvement in GFR.[9] In mixed class ANCA GN, presence of less than 20% cellular crescents in the biopsy sample was associated with a lower one-year GFR by Tanna et al. In his study, the presence of cellular crescents did not correlate with improved GFR. This may be related to the underlying severe chronic changes in sclerotic class ANCA GN.

This study demonstrates that the degree of tubular atrophy correlated with long term renal outcome. Historically chronic tubulo-interstitial lesions have been identified as predictors of adverse renal outcome.[8, 9, 21, 22] Adding interstitial fibrosis and tubular atrophy to enhance the predictive value of ANCA GN classification has yielded variable results. An association between higher degree of tubular atrophy and worse renal outcome was reported by Quintana et al.[19, 23] In the Berden study and in Chinese cohort, there was no correlation of interstitial fibrosis and tubular atrophy with long term renal function.[13, 24]

Patients with sclerotic class GN have adverse prognosis with persistently elevated risk of ESRD or death in multiple cohorts.[13, 14, 25] The one and five year renal survival in validation studies have ranged from 29 to 52% and 29 to 75%.[19, 23, 26] Similar to these studies, we see poor renal and patient survival in our cohort. It may be that in those patients with significant

tubular atrophy, and sclerotic class disease, especially if they are dialysis-dependent on biopsy, that any treatment would prove fruitless. Future studies are needed to evaluate the influence of treatment, particularly in those patients with significant kidney injury at the start of therapy.

We acknowledge that the study is subject to limitations inherent in a retrospective study. Although, the histo-pathological scoring was performed by experienced pathologists, inter-observer variation was not assessed. There are insufficient data to explore the association of plasmapheresis and outcomes in sclerotic class ANCA GN, as well as too few observations for any significant adjustment for potential confounders. Further, as only nine patients experienced relapse over the course of follow-up, there was not sufficient power to model this outcome in any meaningful fashion. The study was enriched with MPO ANCA patients and may not be generalizable to PR3 ANCA patients.

In conclusion, the study demonstrates that renal recovery is rare in patients requiring dialysis at entry despite standard immunosuppression in sclerotic ANCA GN patients. Baseline GFR and tubular atrophy remain as predictors of renal outcome. More information is needed on predictors of treatment response and optimal use of immunosuppression in these patients.

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