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Patient Outcomes in Renal-Limited Antineutrophil Cytoplasmic Antibody Vasculitis With Inactive Histology

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Introduction: Little is known about the anticipated disease course for individuals who present with renal-limited antineutrophil cytoplasmic antibody (ANCA)−associated vasculitis but who lack inflammation on a kidney biopsy. The impact of immunosuppression on renal and overall survival is unknown.

Methods: Patients were recruited from 2005 to 2016 from 8 centers worldwide (N = 16) for this descriptive study. All had positive ANCA, elevated serum creatinine with active urine sediment, histologic evidence of pauci-immune glomerulonephritis without active lesions, and had no evidence of extrarenal vasculitis. We describe the characteristics of this cohort and the differences in the clinical, histologic, and therapeutic parameters of those who developed primary outcomes of end-stage renal disease (ESRD) and vasculitis relapse.

Results: The cohort was 63% Caucasian, and 75% were men, with a median age of 62 years. At entry, the mean $\pm$ SD estimated glomerular filtration rate (eGFR) was 24 $\pm$ 20 ml/min per 1.73 m^2, and 5 patients required dialysis. Twelve patients received immunosuppressive therapy, 25% experienced disease relapse, and 38% developed ESRD. Patients who developed ESRD had lower baseline eGFRs (8 $\pm$ 5 ml/min per 1.73 m^2 vs. 35 $\pm$ 18 ml/min per 1.73 m^2; $P = 0.001$) and more often required dialysis at presentation (83% vs. 0%; $P = 0.001$). Patients who relapsed were less likely to receive immunosuppression (25% for the relapsed group vs. 92% for the nonrelapsed group; relative risk: 0.27, risk difference: 67%; $P = 0.03$).

Conclusion: Among these patients, lower initial eGFR and dialysis dependence at presentation might increase the risk for ESRD. Immunosuppression did not affect renal outcomes in this sample of patients but was associated with a reduced risk for vasculitis relapse. More information is needed on factors that predict treatment response in this high-risk group.

Antineutrophil cytoplasmic antibody (ANCA)−associated vasculitis (AAV) is characterized histologically by small vessel inflammation with few or no immune deposits.[1,2] Renal involvement is initially marked by crescentic glomerulonephritis with fibrinoid necrosis, and over time by glomerular sclerosis, fibrous crescents, and tubulointerstitial fibrosis.[2,3] Various histologic markers carry prognostic significance for renal survival. The percentage of normal glomeruli and active cellular crescents are associated with renal function recovery, but the percentage of global sclerosis, fibrous crescents, and tubulointerstitial disease predict poor outcomes.[2,4–8]

Rarely, the initial biopsy falls outside traditional histologic findings and is devoid of active glomerulonephritis, posing a prognostic and therapeutic dilemma for clinicians. It is believed that such patients experience prolonged subclinical disease, and by the time they present, they have severe renal dysfunction and no symptomatic or histologic evidence of active inflammation. In the setting of apparent irreversible damage and no acute activity, the benefit of an

immunosuppression regimen that carries non-negligible toxicity is unclear. There is currently no data on outcomes or optimal therapy for these patients, and the impact of immunosuppression on renal and overall survival in this population is unknown.

We illustrate a series of patients with renal-limited AAV who presented without systemic evidence of inflammation and who had initial kidney biopsies that were devoid of active glomerulonephritis. The purpose of this study was to describe clinical, histologic, and therapeutic parameters in a group of patients with this rare clinical presentation. As an attempt to gain insight into the role of immunosuppression for these patients, our primary aim was to explore the relationship between receipt of immunosuppression and the development of end-stage renal disease (ESRD) and vasculitis relapse.

METHODS

Study Population

The study population was derived from a retrospective cohort from 8 centers worldwide (Johns Hopkins Hospital Vasculitis Clinic, Baltimore, Maryland, USA; Massachusetts General Hospital, Boston, Massachusetts, USA; Ohio State University, Cleveland, Ohio, USA; Peking University First Hospital, Beijing, China; Trinity Health Kidney Center, Dublin, Ireland; Mount Sinai Hospital, University Health Network, Toronto, Ontario, Canada; and University College London Centre for Nephrology, Royal Free Hospital, London, UK) between 2005 and 2016. Inclusion criteria for this study were the following: presence of clinical evidence of active glomerulonephritis manifested as an increase in serum creatinine, hematuria, and proteinuria; positive ANCA serology; no evidence of active vasculitis on renal biopsy; and absence of symptoms and signs of extrarenal vasculitis. Patients were excluded if they had antiglomerular basement membrane antibodies. The study protocol was approved by the institutional review board at each institution. Sixteen patients were eligible for analysis.

Clinical Data Acquisition

Age, sex, disease phenotype, ANCA serotype, new diagnosis versus established diagnosis, and clinical features at presentation were ascertained. Estimated glomerular filtration rate (eGFR) at presentation, 6 months, and at last follow-up, occurrence of disease relapse, need for renal replacement therapy at the time of presentation and at last follow-up, details of induction therapy, and maintenance immunosuppression were extracted from review of clinical source documents. All kidney biopsies were reviewed to ensure there was no evidence of active renal vasculitis. Adverse events, including new-onset diabetes,

episodes of leukopenia (white blood count <4000/mm^3), and infections that required hospitalization were recorded.

Laboratory Data Acquisition

Serum creatinine at the time of diagnosis was recorded according to the local laboratory. ANCA testing was done by standard indirect immunofluorescence assay on ethanol fixed neutrophils for cytoplasmic ANCA and perinuclear ANCA. Proteinase-3 and myeloperoxidase (MPO) testing by direct enzyme-linked immunosorbent assay were performed according to the local laboratory.

Outcomes

We evaluated outcomes of ESRD and vasculitis relapse during follow-up.

Study Definitions

Disease phenotype was defined according to the Chapel Hill Consensus nomenclature.[1] Renal function was measured using the 4-variable Modification of Diet in Renal Disease formula for eGFR.[9] ESRD was defined by the ongoing need for renal replacement therapy for >3 months. Hematuria was defined as urinary red blood cell count of >5 per high-power field. Kidney involvement was defined by diagnostic renal biopsy. Lack of disease activity was defined by absence of cellular crescents, fibrocellular crescents, and necrotizing lesions on renal biopsy. Interstitial fibrosis was graded as mild, moderate, and severe depending on extent of involvement (<25%, 25%−50%, >50%). Remission was defined as stabilization or improvement in serum creatinine, resolution of hematuria, and absence of extrarenal signs of vasculitis for at least 1 month. Relapse was defined as occurrence of signs and symptoms of vasculitis in any organ that required a change in immunosuppressive therapy after achieving remission.

Statistical Analyses

All descriptive data were presented as median with range or mean ± SD. We described the differences between clinical and histologic parameters between the ESRD groups. Data were tabulated for the full sample and were also divided by ESRD and relapse group. The group differences were tested using Student's t-test and Fisher exact tests. All tests of significance were 2-sided, and differences were considered significant if the P value was <0.05.

RESULTS

Patient Characteristics

Table 1 shows baseline patient characteristics. All patients presented with new-onset vasculitis. One patient

Table 1. Patient characteristics at initial disease presentation

Patient characteristic	Distribution
Median age at presentation, yr	62 (40–76)
Median follow-up (mo)	11 (1–127)
Men	75 (12)
Race	
Caucasian	63 (10)
Asian (Chinese)	37 (6)
Black	0 (0)
Other	0 (0)
ANCA category	
MPO positive	88 (14)
PR3 positive	12 (2)
Initial eGFR, ml/min per 1.73 m^2	24 ± 20
Dialysis at diagnosis	31 (5)
No. of glomeruli in biopsy	28 ± 16
Normal glomeruli on biopsy, %	16 ± 25
Glomeruli with fibrous crescents, %	27 ± 26
Glomeruli with global sclerosis, %	47 ± 32
Induction immunosuppression	75 (12)
Pulse methylprednisolone	6
Cyclophosphamide	9
Rituximab	3
Developed ESRD, %	38 (6)
Disease relapse	25 (4)
Infections	38 (6)
Death during follow-up	25 (4)

ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MPO, myeloperoxidase; PR3, proteinase-3.
Values are median (range), % (no.), or mean ± SD.

presented with subacute weight loss, but otherwise, these individuals lacked systemic symptoms, and clinical presentations were limited to acute kidney injury (AKI) with active urinary sediment. Median age at time of initial biopsy was 62 years (range: 40–76 years). Eighty-eight percent of patients were positive for MPO-ANCA. Mean ± SD eGFR was 24 ± 20 ml/min per 1.73 m^2, and 5 patients (31%) required dialysis at presentation.

Mean ± SD sampled glomeruli was 28 ± 16. All biopsy specimens were devoid of fibrinoid necrosis, cellular crescents, and fibrocellular crescents. Mean ± SD normal glomeruli was 16 ± 25%, percentage of global sclerosis was 47 ± 32%, and 27 ± 26% of glomeruli exhibited fibrous crescents. All biopsies had moderate to severe interstitial fibrosis and tubular atrophy, with 9 revealing severe interstitial fibrosis and tubular atrophy.

Induction immunosuppression was given to 12 patients (75%); 6 received initial pulse methylprednisolone, and 9 and 3 received cyclophosphamide and rituximab, respectively. Of the 12 patients, 4 were dialysis-dependent at entry, and the remaining 8 patients had a baseline mean ± SD eGFR of 30 ± 19 ml/min per 1.73 m^2. No patient received plasmapheresis. Information on duration of steroid use was available for 9 patients; median duration was 12 months (range:

1–108 months). Information on duration of cyclophosphamide use was available for 8 patients; the median duration was 1.5 months (range: 1–50 months). There were no reported cases of new-onset diabetes or leukopenia, although information for these variables was only available for 14 patients. Six patients (38%) experienced infections that required hospitalization; all of these patients received immunosuppression. Four (25%) patients died; 2 from infection, 1 from an unknown cause, and another from unrelated head trauma.

Outcomes

Throughout a median follow-up period of 22 months (range: 1–127 months), 6 patients (38%) developed ESRD. Clinical, histologic, and therapeutic characteristics of the ESRD and non-ESRD groups are shown in Table 2. There were no significant differences in age, race, or ANCA type. Patients who developed ESRD had a lower baseline eGFR (8 ± 5 ml/min per 1.73 m^2 vs. 35 ± 18 ml/min per 1.73 m^2; $P = 0.001$). Patients who developed ESRD were also more likely to be on dialysis at presentation (83% vs. 0%; $P = 0.001$). None of the patients who initially required dialysis recovered renal function. The percentage of global sclerosis was higher in the ESRD group than in the non-ESRD group (62 ± 31% vs. 38 ± 31%; $P = 0.17$), and the non-ESRD group had more normal glomeruli than the ESRD group (21 ± 30%; $P = 0.25$), but these findings were not statistically significant. The 2 groups did not differ with respect to the percentage of fibrous crescents or degree of interstitial fibrosis and tubular atrophy, receipt of immunosuppression, infection rate, or mortality. Of the 4 patients who were dialysis-dependent at entry and received induction therapy, none recovered renal function. Of the 8 patients who did not require dialysis at entry and received immunosuppression, the mean ± SD eGFR at 1 year was 34 ± 23 ml/min per 1.73 m^2 in 6 patients. One patient did not have a follow-up serum creatinine at 1 year, and the other patient died due to infection.

Four patients experienced disease relapse (at 2, 12, 13, and 69 months after initial biopsy). Relapses consisted of cutaneous manifestations, pulmonary hemorrhage, and recurrent AKI, with active cellular crescents on repeat kidney biopsy. Table 2 displays characteristics of the 2 relapse groups. Those who relapsed were less likely to have received immunosuppression than those who did not relapse (25% vs. 92%; relative risk: 0.26; risk difference: 67%; $P = 0.03$). Only 1 of 12 patients who received immunosuppression relapsed; this patient received cyclophosphamide for 1 month before stopping therapy and then developed pulmonary hemorrhage 1 month later. The 2 groups did not differ with respect to age, race, ANCA type, presenting

Table 2. Comparison of patient characteristics according to primary outcomes of ESRD and vasculitis relapse

Patient characteristic	ESRD (n = 6)	No ESRD (n = 10)	P value	Relapse (n = 4)	No relapse (n = 12)	P value
Median age at biopsy, yr	56 (40–70)	62 (49–76)	0.31	63 (49–76)	59 (40–73)	0.43
White race	83 (5)	50 (5)	0.31	75 (3)	58 (7)	1.0
MPO-ANCA	90 (9)	83 (5)	1.0	100 (4)	83 (10)	1.0
eGFR at biopsy, ml/min per 1.73 m^2	8 ± 5	35 ± 18	0.001	34 ± 20	21 ± 19	0.30
Dialysis at diagnosis	85 (5)	0 (0)	0.001	25 (1)	33 (4)	1.0
Global sclerosis, %	62 ± 31	38 ± 31	0.17	38 (25)	50 (35)	0.49
Fibrous crescents, %	27 ± 22	27± 30	0.97	27 (32)	27 (26)	0.97
Normal glomeruli, %	7 ± 12	21 ± 30	0.25	24 (18)	13 (27)	0.39
Received induction immunosuppression, %	83 (5)	70 (7)	1.0	25 (1)	92 (11)	0.03
Cyclophosphamide	50 (3)	60 (6)	1.0	25 (1)	67 (8)	0.26
Rituximab	30 (2)	10 (1)	0.52	0 (0)	25 (3)	0.53
Infections	33 (2)	50 (4)	1.0	75 (3)	30 (3)	0.12
Died	33 (2)	25 (2)	0.6	25 (1)	30 (3)	1.0

ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MPO, myeloperoxidase.
Values are median (range), % (no.), or mean ± SD.

eGFR, initial dialysis requirement, specific induction regimen, infection risk, or mortality.

DISCUSSION

Overall, we found no significant relationship between receipt of induction immunosuppression and renal recovery. However, those who received immunosuppression were less likely to relapse. Like the general population with renal-limited AAV, those with a lower eGFR had an increased risk for ESRD. Histologic characteristics thought to carry prognostic significance were not of great value in these patients.[2,4–7,10]

The decision to use immunosuppressive therapy in patients without histologic or systemic evidence of disease activity is complex. One of our primary aims was to begin to describe the possible risks and benefits of immunosuppression in the absence of identifiable inflammation. In patients with active biopsy lesions, there was similar debate in the past about the threshold of renal damage, at which point the chance of renal recovery with immunosuppression might be deemed futile. Several groups independently found that a substantial proportion of patients who initially required dialysis recovered, and concluded that a trial of immunosuppression with glucocorticoids and cyclophosphamide should be considered regardless of renal function at diagnosis.[11–13] Lee et al. evaluated patients who presented with eGFR <15 ml/min per 1.73 m^2, and found that even among those with maximal chronicity index scores, the probability of treatment response was >14%.[11] Hogan et al. reported that more than one-half of those who presented with eGFR <10 ml/min reached remission with immunosuppression treatment.[12] However, the patients in these studies all had clear evidence of active inflammation at presentation.

Unlike existing literature, our findings suggested that immunosuppression might not alter renal outcomes in the absence of identifiable inflammation.[11,12,14] However, those who receive immunosuppression at presentation might be less likely to experience relapse (with renal and extrarenal organ involvement) than patients who do not receive immunosuppression. We recommend this consideration be factored into decision making and included in treatment discussions with patients. We cannot comment on the choice and duration of therapy because this was determined by the local physician and therefore highly variable. We were not able to analyze the impact of steroid or cyclophosphamide duration on outcomes due to missing information on these variables.[15] We also could not comment on the role of plasmapheresis in these patients, because most presented at a time when plasmapheresis was primarily restricted to those with severe pulmonary hemorrhage and was not routinely used for severe renal dysfunction.[16]

The benefit of relapse prevention should be weighed against the risk of infection in the individual. In this sample, infections occurred in both immunosuppression groups (8% risk difference between the immunosuppressed group and nonimmunosuppressed group; P = 0.57). Infections in the immunosuppressed group occurred after 1, 6, 12, and 20 months of therapy. All immunosuppressed patients received appropriate infection prophylaxis, and there were no cases of preventable infection (such as with Pneumocystis jiroveci pneumonia).

Our findings agreed with past studies on the relationship between initial renal function and renal survival. In 2003, Vergunst et al. found that initial eGFR was the strongest predictor of renal function at 1 year.[8] In 2010, Berden et al. found that baseline eGFR was an

independent predictor for renal function at 1 and 5 years.[2] Initial dialysis dependence and increased risk for ESRD was also previously reported, although this might be a property of renal-limited disease and not a reflection of histologic phenotype.[3,4] Neumann *et al.* evaluated patients with ANCA glomerulonephritis who were dialysis-dependent at presentation, and reported that fewer patients with renal-limited disease recovered renal function than those with extrarenal disease.[4] This was attributable to the often delayed diagnosis in these patients due to the absence of extrarenal manifestations.

Two histologic characteristics trended toward increased risk for ESRD. The percentage of normal glomeruli on initial biopsy was consistently associated with favorable renal outcome, and was shown to be predictive of need for dialysis at 12 months.[4,10] In this study, the non-ESRD group had a greater percentage of normal glomeruli than the ESRD group, but this finding was not statistically significant. A high percentage of sclerotic glomeruli was also repeatedly linked to poor renal outcomes.[2,6,7,17] Bajema *et al.* examined renal biopsies in patients with systemic vasculitis, and found a correlation between the percentage of global sclerosis and serum creatinine 1 year later ($P < 0.0005$).[7] Hauer *et al.* similarly found a correlation between percentage of glomerulosclerosis and eGFR at 18 months ($r = -0.37$).[6] In this study, the ESRD group had a higher mean percentage of sclerotic lesions, but again, this was not statistically significant. These findings could be due to inadequate sample size, and perhaps with more patients, our findings would agree with existing literature on patients with ANCA glomerulonephritis.

Limitations in this study reflected the overall rarity of this patient population. Importantly, there was no comparison group, and our findings should be interpreted as preliminary and descriptive in nature. Due to the small number of patients in this sample, our comparisons were underpowered to detect differences between the ESRD and relapse groups. Data were collected from several centers worldwide, and laboratory measures were nonuniform. There was no established protocol on the therapeutic regimens used. This prevented extrapolation of information regarding specific immunosuppression regimens.

In conclusion, renal function and dialysis dependence at presentation might increase risk for ESRD in patients with renal-limited AAV and inactive histology. Immunosuppression did not affect renal outcomes in this sample of patients, but was associated with reduced risk for vasculitis relapse. More information is needed on the optimal use of immunosuppression in this population.

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65:1–11.

2. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628–1636.

3. Cordova-Sanchez BM, Mejia-Vilet JM, Morales-Buenrostro LE, Loyola-Rodriguez G, Uribe-Uribe NO, Correa-Rotter R. Clinical presentation and outcome prediction of clinical, serological, and histopathological classification schemes in ANCA-associated vasculitis with renal involvement. *Clin Rheumatol*. 2016;35:1805–1816.

4. Neumann I, Kain R, Regele H, Soleiman A, Kandutsch S, Meisl FT. Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. *Nephrol Dial Transplant*. 2005;20:96–104.

5. Hauer HA, Bajema IM, Hagen EC, et al. Long-term renal injury in ANCA-associated vasculitis: an analysis of 31 patients with follow-up biopsies. *Nephrol Dial Transplant*. 2002;17:587–596.

6. Hauer HA, Bajema IM, Van Houwelingen HC, et al. Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int*. 2002;62:1732–1742.

7. Bajema IM, Hagen EC, Hermans J, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int*. 1999;56:1751–1758.

8. Vergunst CE, van Gurp E, Hagen EC, et al. An index for renal outcome in ANCA-associated glomerulonephritis. *Am J Kidney Dis*. 2003;41:532–538.

9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.

10. de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol*. 2006;17:2264–2274.

11. Lee T, Gasim A, Derebail VK, et al. Predictors of treatment outcomes in ANCA-associated vasculitis with severe kidney failure. *Clin J Am Soc Nephrol*. 2014;9:905–913.

12. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med*. 2005;143:621–631.

13. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol*. 1996;7:33–39.

14. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev*. 2015: CD003232.

15. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum*. 1997;40:2187–2198.

16. Walsh M, Casian A, Flossmann O, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int*. 2013;84:397–402.

17. Neumann I, Regele H, Kain R, Birck R, Meisl FT. Glomerular immune deposits are associated with increased proteinuria in patients with ANCA-associated crescentic nephritis. *Nephrol Dial Transplant*. 2003;18:524–531.