Renal Transplant in Wegener's Granulomatosis Compared to Microscopic Polyangiitis

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ABSTRACT. ***Objective.*** Antineutrophil cytoplasmic antibody-associated vasculitis is an important cause of endstage renal disease. Our aim was to investigate how the underlying vasculitis diagnosis may influence outcomes following renal transplant.

Methods. We undertook a retrospective cohort study of patients who underwent renal transplant at the Johns Hopkins Hospital between 1999 and 2008.

Results. Detailed followup data were available for 11 patients with Wegener's granulomatosis (WG) and 6 with microscopic polyangiitis (MPA), representing 799 patient-months of observation. Patients with WG remained on hemodialysis longer (and may have had slightly worse renal outcomes following transplant) than patients with MPA. Four patients with WG experienced adverse events following renal transplant: 2 experienced rejection and 2 vasculitis flare. Among the patients with MPA, there was 1 episode of rejection and no vasculitis flare.

Conclusion. Whether outcomes following renal transplant may be influenced by the underlying diagnosis of vasculitis merits further study. (First Release June 1 2010; J Rheumatol 2010;37:1705–8; doi:10.3899/jrheum.091202

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODY VASCULITIS KIDNEY TRANSPLANT MICROSCOPIC POLYANGIITIS WEGENER'S GRANULOMATOSIS

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are the most common cause of rapidly progressive glomerulonephritis-induced endstage renal disease[1]. Renal transplant has become an important therapeutic option for these patients, but data on outcomes after renal transplant are limited[2].

The AAV tend to be considered together in renal transplant studies, which often assume that patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) will have similar outcomes after transplant. However, renal outcomes and the risk of relapse associated with these diseases vary substantially[3,4,5]. It therefore seems reasonable to question whether patients with WG or MPA might have substantially different outcomes following renal transplant. We report our experience with WG and MPA patients following renal transplant.

MATERIALS AND METHODS

Records of all patients transplanted at The Johns Hopkins Hospital, Baltimore, MD, between 1999 and 2008 were reviewed. Patients with a diagnosis of vasculitis as cause of endstage renal disease were selected. Records were evaluated to confirm that all patients met Chapel Hill Consensus Conference criteria for WG or MPA[6]. The following clinical data were extracted: age, sex, type of transplant, time spent on dialysis, relapse on dialysis, ANCA serology at time of transplant, episodes of vasculitis relapse, episodes of rejection, and serum creatinine 12, 24 and 60 months posttransplant. Analysis was performed using Stata 9.0 (Stata Corp., College Station, TX, USA).

RESULTS

Between January 1999 and December 2008, 1678 kidney transplants were performed at The Johns Hopkins Hospital. Twenty-four of these patients had developed endstage renal disease due to WG or MPA. Detailed followup data are available for 11 patients with WG and 6 with MPA, representing 799 patient-months of observation. The median period of observation for each patient was 37 months: 31 months for patients with MPA, 57 months for patients with WG. This patient cohort included 3 African American patients with WG; all other subjects were Caucasian (82.4%). The overall gender distribution was equal (Table 1).

All patients but one (94.1%) had renal involvement as part of their initial presentation; 5 WG patients (45.5%) and 2 MPA patients (33.3%) presented with endstage renal disease. Two patients with WG and one with MPA received preemptive kidney transplants. Three patients with WG had previously received a renal transplant. Most patients in this cohort received a renal transplant from a living related donor (70.6%). At time of transplant, patients with WG were older (median age 52 vs 39 yrs in MPA) and carried a diag-

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Table 1. Baseline demographic and clinical data in patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).

Patient	Age, yrs	Sex	Diagnosis	Phenotype	Duration of Dialysis, mo	Renal Transplant	ANCA Type at Diagnosis	ANCA Status at Transplant
1	35	F	WG	ENT, L, K	24	LR	C-ANCA	Not available
2	65	M	WG	ENT, J, K	18	LR	C-ANCA	Positive
3	39	M	WG	ENT, K, L, S	45	LR	C-ANCA	Positive
4	39	F	WG	ENT, K	48	LUR	C-ANCA	Negative
5	42	M	WG	ENT, J, K	48	LR	C-ANCA	Negative
6	62	M	WG	Eye, J, K	12	LR	C-ANCA	Negative
7	44	F	WG	ENT, S, K, L	12	LR	C-ANCA	Negative
8	31	F	WG	K, J	72	LR	C-ANCA	Positive
9	29	M	WG	J, K, L	Preemptive	LR	C-ANCA	Negative
10	34	F	WG	ENT, K	18	DD	Negative	Negative
11	56	M	WG	ENT, K, L, S	Preemptive	DD	C-ANCA	Positive
12	23	F	MPA	K, L	1	LR	P-ANCA	Negative
13	47	M	MPA	K	12	LR	P-ANCA	Not available
14	58	M	MPA	K	Preemptive	LR	P-ANCA	Negative
15	70	F	MPA	K, L	20	LR	P-ANCA	Negative
16	56	F	MPA	K, L	14	LR	P-ANCA	Positive
17	39	F	MPA	K, L	15	LUR	C-ANCA	Negative

ANCA: antineutrophil cytoplasmic antibody; LR: living related; LUR: living unrelated; DD: deceased donor: ENT: sinus, ear: K: kidney, L: lung; S: skin; J: joint.

nosis of vasculitis for longer (51 vs 18.5 mo in MPA) than patients with MPA, although the difference was not statistically significant ($p = 0.2$ for each comparison). Patients with WG continued hemodialysis longer than did patients with MPA (median time on dialysis 24 vs 18 mo, respectively; $p = 0.10$).

Renal transplant outcomes. Three of the WG patients were highly sensitized from prior kidney transplants and blood transfusions, and had a positive crossmatch with their donors. They received treatment with plasmapheresis and intravenous immunoglobulin 1 week prior to transplant; 1 patient also received rituximab before transplant to suppress donor-specific antibodies. Six patients received antibody induction therapy: 5 received antithymocyte globulin and 1 was treated with daclizumab. All patients received maintenance immunosuppression with mycophenolate mofetil 2 g daily, tacrolimus, and prednisone 5 mg daily.

There were no episodes of rejection among patients with MPA. Two of the 3 highly sensitized patients with WG had an episode of biopsy-proven rejection; one of these patients continues to have allograft dysfunction due to chronic rejection. One patient with WG had biopsy-proven BK virus-associated nephropathy 6 months after transplant. There were no episodes of graft loss in this series.

The median serum creatinine concentration following transplant was 1.1 mg/dl among patients in both groups. At the last followup, the median serum creatinine among patients with WG had increased to 1.3 mg/dl, but it did not change substantially among patients with MPA (1.0 mg/dl; $p = 0.1$; Figure 1).

Vasculitis outcomes and risk of relapse. Most patients (10/16) were ANCA-negative at the time of transplant; none

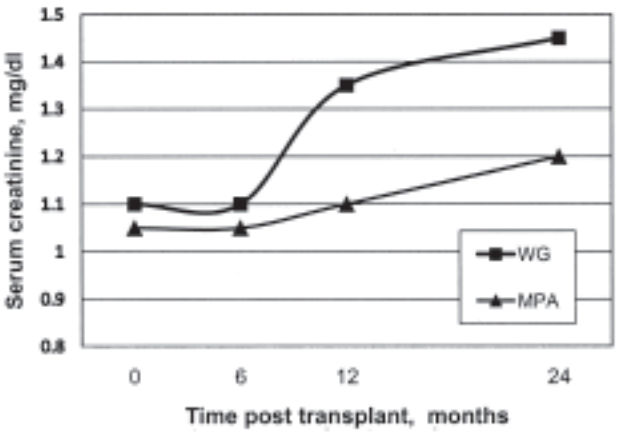

Figure 1. Renal function among patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) after renal transplant. Median serum creatinine 0, 6, 12, and 24 months after transplants.

of these patients have experienced a vasculitis flare during the observation period. There was one vasculitis flare per 200 patient-years of observation (equivalent to a flare rate of 0.005 per patient per year). All flares occurred in the presence of detectable circulating ANCA: one patient with MPA developed necrotizing glomerulonephritis of the transplanted kidney 3 months after transplant that responded to a 3-month course of cyclophosphamide. Another patient with WG developed 2 episodes of a pulmonary-renal hemorrhage syndrome 45 months and 55 months after transplant; the latter occurred in the setting of noncompliance with his immunosuppression. A third patient with WG developed a vasculitis flare involving only the joints 3 years after transplant. Of these patients, only one received induction therapy

(with thymoglobulin). None of the remaining patients experienced either renal or extrarenal relapse of vasculitis after transplant after a median observation period of 37 months (Table 2).

DISCUSSION

Rapidly progressive deterioration of renal function is a common consequence of the AAV. Up to 20% of patients develop endstage renal disease[7,8,9]. As the overall outcomes of patients with AAV improve, issues pertaining to renal transplantation will become increasingly important for this patient population.

Kidney transplant in AAV has traditionally been associated with a high rate of vasculitis flare. Individual case series describe a relapse rate ranging from 11% to 50%[8,10,11,12,13,14]. This case series is remarkable for the low rate of renal and extrarenal vasculitis flares following transplant, which may be due to the use of mycophenolate mofetil and tacrolimus in combination. It is notable that this relapse rate is lower than that reported with use of mycophenolate mofetil alone in WG patients in nontransplant settings[15].

There is strong evidence that the presence of circulating ANCA does not preclude successful renal transplantation[2,10,12]. However, in this patient cohort, ANCA-negativity at the time of transplant seemed to predict a more quiescent clinical course. It is also interesting that patients with WG waited longer for transplant and had worse renal function following transplant than patients with MPA. Although these differences were small, they highlight the possibility that rheumatologists may be reluctant to consider WG patients for renal transplantation, which may influence longterm transplant outcomes. This also raises the intriguing possibility that, despite similarities in etiopathogenesis, subjects with WG are at greater risk for rejection than patients with MPA. This possibility may be obscured by transplant databases, which often conflate these diagnoses. Future transplant research will need to include careful phenotyping of these patients in order to clarify this important issue.

We have described a cohort of patients with WG and MPA who have had excellent graft survival rate and a lower rate of vasculitis relapse than reported in other series[2,9,14]. It is tempting to speculate that a mycophenolate mofetil/tacrolimus-based regimen may be more effective than other immunosuppressive regimens for patients with AAV who undergo kidney transplant. The possibility that patients with WG may have worse renal outcomes after transplant than patients with MPA also merits further study.

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Table 2. Posttransplant outcomes among patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA).

Patient	Duration of Followup, mo	Diagnosis	Rejection	Relapse Posttransplant	Baseline Serum Creatinine, mg/dl	Serum Creatinine at 12 mo, mg/dl	Serum Creatinine at Last Followup, mg/dl
1	24	WG	N	N	0.7	0.8	0.8
2	60	WG	N	Y	1.2	1.6	1.4
3	52	WG	N	Y	1.3	1.6	1.7
4	37	WG	Y	N	1.0	1.3	5.7
5	79	WG	N	N	1.3	1.4	1.4
6	70	WG	N	N	1.2	1.1	1.2
7	73	WG	N	N	1.0	1.0	0.9
8	25	WG	Y	N	1.4	1.7	1.7
9	12	WG	N	N	1.5	1.5	1.5
10	93	WG	N	N	0.6	0.7	0.7
11	7	WG	N	N	1.0	NA	0.9
12	29	MPA	N	N	0.9	1.0	1.0
13	80	MPA	N	Y	1.7	1.8	1.6
14	25	MPA	N	N	1.5	1.5	1.5
15	32	MPA	N	N	1.0	1.1	0.9
16	27	MPA	N	N	1.1	1.1	1.1
17	24	MPA	N	N	1.1	1.1	0.9

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