Transpl Int (1997) 10: 152–156

BRIEF REPORT

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Single-center experience with renal transplantation in patients with Wegener's granulomatosis

Received: 1 July 1996
Received after revision: 6 September 1996
Accepted: 23 September 1996

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Abstract Between 1980 and 1995, 13 patients with end-stage renal disease due to Wegener's granulomatosis received 14 renal transplants (10 cadaveric, 4 living related). The mean follow-up in the 13 successfully transplanted patients was 50 months (4–107 months). One patient had primary nonfunction and received another graft 4 months later. Three episodes of acute rejection occurred in two patients, and one of these patients lost her graft due to severe vascular rejection 4 months after transplantation. Two patients died with well-functioning grafts (one of metastatic cancer and one of sepsis). One patient presented with perisinusitis and had a mild recurrence of Wegener's disease. None of the patients developed recurrent disease in the transplanted organ. At the last follow-up, the mean creatinine (± SD) in the 12 patients with functioning grafts was 1.6 ± 0.6 mg/dl. We conclude that renal transplantation is an excellent treatment for renal failure due to Wegener's granulomatosis. Recurrence of the disease is uncommon in patients under immunosuppression, but careful monitoring is extremely important.

Key words Kidney transplantation, Wegener's granulomatosis · Wegener's granulomatosis, Kidney transplantation

Introduction

Wegener's granulomatosis is a rare disease characterized by granulomatous vasculitis and glomerulonephritis involving the upper and lower respiratory tract, joints, skin, and kidneys. Renal involvement occurs in approximately 85 % of the patients [8]. Though this condition was previously uniformly fatal, the prognosis has been much improved by the use of immunosuppressive and cytotoxic agents. Following aggressive treatment of the disease with glucocorticoids and cyclophosphamide, only a small number of patients develop end-stage renal failure. In the largest reported series of 158 patients, 11 % (17 patients) eventually required dialysis (some of these only temporarily) and 5 % (8 patients) underwent renal transplantation (Tx) [10]. Successful renal Tx in these patients has been reported in a number of cases [7, 10, 13, 22, 27]. Although immunosuppressive treatment after Tx seems to control the disease activity, several cases of severe recurrent disease manifestations have been described in the literature [1, 2, 6, 15, 18–21, 25, 26]. To further identify the risk of recurrence in an unselected patient population, we describe our single-center experience in all patients with Wegener's granulomatosis who underwent renal Tx at a university-based hospital.

Case reports

Between 1980 and 1995, 3942 kidneys were transplanted at the University of Wisconsin Hospital. Among the recipients were 13 patients (6 male and 7 female; mean age at Tx 46.3 ± 14.5 years) with Wegener's granulomatosis who received 14 kidney trans-

Table 1 Demographic data for patients with Wegener's granulomatosis who received kidney transplants [*RTx* renal transplantation, *P* pulmonary involvement, *R* renal involvement, *N* nasal, sinus, and/or eye involvement, *A* arthropathy (joint pain), *pred* prednisone, *cp* cyclophosphamide]

Patient no.	Age at transplantation (month/year of RTx)	Sex	First organ involved	Renal symptoms (months prior to RTx)	Treatment prior to RTx	Dialysis therapy (months prior to RTx)
1A	61 (07/87)	F	P, R	139	pred, cp	10
1B	62 (11/87)	F	P, R	143	pred, cp	14
2	54 (07/91)	M	R	55	pred, cp	19
3	25 (10/90)	M	P	16	pred, cp	16
4	65 (11/95)	F	R	35	pred, cp	29
5	37 (11/89)	F	P, R, N	47	pred, cp	47
6	54 (09/91)	M	P, N, A	45	pred, cp	0
7	42 (03/94)	M	P, R	132	pred, cp	10
8	35 (08/95)	F	P, R	33	pred, cp	28
9	58 (09/91)	F	P, R, N, A	59	pred, cp	12
10	17 (02/90)	F	P, R	96	pred, cp	6
11	52 (08/80)	M	R	39	pred, cp	39
12	38 (07/88)	M	R, A	12	pred, cp	12
13	48 (12/89)	F	P	44	pred, cp	44

plants. Since Wegener's granulomatosis is a distinct clinicopathological entity, the disease was diagnosed in our patients primarily according to the criteria of the American College of Rheumatology [14]. Renal involvement as part of the first manifestation of the disease was seen in 10 of the 13 patients (Table 1). The first renal symptoms of the disease occurred 63.9 ± 44.8 months (mean ± SD) before Tx. All patients had been treated with cyclophosphamide and tapering steroids, and showed sustained remissions, especially with respect to the disease manifestations in the lower and/or upper respiratory tract. All patients eventually developed chronic renal disease – after a temporary stabilization of kidney function in some cases – and progressed to end-stage renal failure. Twelve patients had been on dialysis prior to Tx for a mean of 17.2 ± 13.8 months (Table 1), while one patient with slowly progressing renal failure received a cadaver kidney without dialysis.

Nine patients received ten cadaver kidneys, while four patients received kidneys from living related donors (Table 2). Patient 1A showed primary nonfunction secondary to cortical necrosis of the cadaver kidney and received another transplant 4 months later. Immunosuppressive induction treatment with Minnesota antilymphocyte globulin (MALG) was given in 13 transplantations; one patient with a haploidentical living related transplant did not receive induction therapy (patient 12). Instead, this patient received maintenance immunosuppression consisting of prednisone (10 mg/day), cyclosporin A (5 mg/kg per day) and cyclophosphamide (100 mg/day). Eleven of the 12 remaining recipients received maintenance immunosuppression consisting of triple therapy: 10 mg/day prednisone, 4–6 mg/kg per day cyclosporin A, and 50–100 mg/day azathioprine or 2000–3000 mg/day mycophenolate mofetil. The remaining patient (no. 11) was treated with 10 mg/day prednisone and 150 mg/day azathioprine.

The mean follow-up for all 13 patients with postoperative functioning grafts was 49.9 ± 32.0 (4–107) months (Table 2). Two patients died with functioning grafts secondary to causes not related to Wegener's granulomatosis. Patient 11 developed a carcinoma of his parotic gland and died 28 months after Tx of metastatic disease. Patient 12 developed an acute abdomen 64 months afterTx. Laparotomy showed necrosis of the colon with perforation, and death occurred due to severe sepsis 7 days later. Pathohistological examination showed a picture consistent with pseudomembranous colitis. There was no evidence of Wegener's disease. The creatinine level at admission was 2.2 mg/dl, and the titers of antineutrophil cytoplasmic antibodies (cANCA and pANCA) were negative.

Other medical complications were infrequent. Two of 13 patients had three biopsy-proven acute rejection episodes. One lost his graft 4 months after Tx secondary to severe vascular rejection that was refractory to therapy with monoclonal anti-CD3 antibodies (OKT3). Other complications included severe hypertension in three patients. One patient had peripheral stenosis of one of two renal transplant arteries in which angioplasty was not successful. Another patient developed biopsy-proven cyclosporin toxicity. Recurrent urinary tract infections were present in another patient. The most recent reading of serum creatinine in the 12 patients with functioning grafts (including the patients who died with a functioning graft) was 1.6 ± 0.6 mg/dl. The most recent reading of the blood urea nitrogen (BUN) level was 25 ± 8 mg/dl. No patient developed recurrent disease in the allograft.

One of the 13 patients presented with the clinical and radiological picture of perisinusitis 67 months after Tx, which raised the suspicion of a mild recurrence of Wegener's disease without biopsy-proven recurrence. These symptoms were resolved with a short course of tapering prednisone (starting with 30 mg/day) and the administration of trimethoprim sulfamethoxazole. Unfortunately, no ANCA level was measured at this time.

Discussion

After renal Tx was first described as treatment for end-stage renal failure secondary to Wegener's granulomatosis in 1972 [16], it became a commonly accepted pro-

Table 2 Clinical outcome of 13 recipients receiving 14 renal transplants (*CAD* cadaveric donor, *LRD* living related donor, *Pred* prednisone, *Aza* azathioprine, *CyA* cyclosporin A, *MMF* mycophenolate mofetil, *cp* cyclosphosphamide)

Patient no.	Donor graft	Graft function (months)	Immuno-suppression	Outcome
1 A	CAD	0	Pred, Aza	Primary nonfunction (cortical necrosis)
1 B	CAD	107	Pred, Aza, CyA	Recurrence: sinusitis 67 months post-Tx
2	CAD	59	Pred, Aza, CyA	
3	CAD	74	Pred, Aza, CyA	
4	LRD	7	Pred, MMF, CyA	
5	CAD	79	Pred, Aza, CyA	
6	CAD	57	Pred, Aza, CyA	
7	CAD	27	Pred, Aza, CyA	
8	LRD	10	Pred, MMF, CyA	
9	CAD	57	Pred, Aza, CyA	
10	LRD	76	Pred, Aza, CyA	
11	CAD	28	Pred, Aza	Death 28 months post-Tx with functioning graft due to metastatic cancer of the parotic gland
12	LRD	64	Pred, cp, CyA	Death 64 months post-Tx with functioning graft due to sepsis and pseudomembraneous colitis
13	CAD	4	Pred, Aza, CyA	Graft failure due to acute vascular rejection 4 months post-Tx

cedure in these patients [7, 8, 13]. Wegener's disease is rare. Between 1987 and 1994, 114 transplant patients with this diagnosis who received a cadaveric graft and 61 who received a graft from a living donor were reported to the United Network for Organ Sharing (UNOS). The 1-year and 3-year graft survival rates were 90.2 % and 77.8 %, respectively, for recipients of a cadaveric graft and 96.6 % and 84.0 %, respectively, for those with a living donor graft [3]. Over the past several years, numerous case reports about recurrent disease involving either the upper and lower respiratory tract or the transplanted graft have appeared in the literature [1, 2, 4, 6, 9, 12, 15, 18–21, 24–26]. Recurrence occurred under different maintenance immunosuppression protocols, e.g., prednisone and cyclosporin A [18, 20], azathioprine and prednisone [6], and triple therapy with cyclosporin A, azathioprine, and prednisone [1, 2, 12, 15, 21, 26].

Recent reports suggest that cyclosporin A effectively controls active renal and extrarenal Wegener's granulomatosis in primary treatment and in patients who have previously failed cytotoxic therapy [4, 23]. Cyclosporin A has also been used as maintenance immunosuppression in transplant recipients with Wegener's disease without evidence of recurrent disease, successfully preventing rejection [11, 22]. Other reports suggest that disease recurrence occurs earlier in patients treated with cyclosporin A as opposed to azathioprine, but that rejection occurs more often after azathioprine/prednisone therapy without cyclosporin A [4, 21, 26]. In a recent report of recipients under triple therapy, severe relapses were observed, leading to a graftectomy in one case [15].

In contrast, 12 of our 13 patients received triple maintenance immunosuppression, and in only one of these cases was a mild recurrence suspected. We observed three episodes of acute rejection in two patients, which led to graft loss in one case secondary to treatment of refractory vascular rejection. The risk of rejection in these recipients appears to be similar to the rejection incidence in the general kidney transplant population. This finding is in agreement with other reports [13, 22, 27].

Tzardis et al. reported a good long-term survival in eight patients with Wegener's granulomatosis [27]. Similar to our observation, there was only one mild recurrence in one case (perisinusitis 4 months after Tx). In contrast to our population, seven of the eight patients in their study received a living related organ, whereas the majority of our patients (9 of 13) had cadaveric transplants. The immunologic graft loss in one of our patients happened in a cadaver kidney recipient, whereas

no graft loss was observed in Tzardis' group. However, one death secondary to a cause other than Wegener's granulomatosis was reported.

A recently published experience including 20 patients from two centers noted one death 48 months after Tx due to a severe relapse involving the lungs and gastrointestinal tract, but not the kidney [22]. Five of the 20 patients had seven relapses, mainly in the upper and lower respiratory tract. Immunosuppression consisted of cyclosporin and prednisone in 15 of the 20 patients, while 5 patients received triple therapy (either with azathioprine or cyclophosphamide). The rate of recurrent disease in this group was higher than in our patients, which may reflect the effectiveness of triple therapy in suppressing the disease activity.

Whether post-transplant immunosuppression should include cyclophosphamide as maintenance therapy is unclear. Long-term treatment with cyclophosphamide seems to be associated with a higher risk of side effects (e.g., bone marrow suppression, bladder cancer, and lymphomas) than treatment with other immunosuppressants [10]. It is remarkable that our patient who died of sepsis 64 months after Tx was the only patient who received cyclophosphamide within his immunosuppressive treatment. Since successfully achieved remissions in recurrent Wegener's granulomatosis after Tx have been reported after reintroduction of cyclophosphamide [2, 4, 25], it has been suggested that the immunosuppressive treatment should include cyclophosphamide only in cases with suspected recurrent disease [21, 22].

In several case reports, elevated ANCA levels at the time of disease recurrence were noted [1, 18, 21, 26]. In patients without transplants but with Wegener's granulomatosis, treatment with cyclophosphamide based on rising ANCA levels prior to development of a clinically overt relapse has been described, and has led to a successful prevention of relapses [5]. However, ANCA levels have been reported to be positive in approximately 30 % of patients in complete remission [17]. Recently, a case with a rapid catastrophic onset of Wegener's granulomatosis in the renal graft without increasing ANCA levels was published [20]. Therefore, clinical presentation appears to be a stronger indicator of recurrence in transplant recipients under maintenance immunosuppression than ANCA levels alone. However, serial ANCA measurements after Tx may be an additional tool for the early diagnosis of Wegener's disease relapses.

In summary, renal Tx is an excellent treatment for patients with end-stage renal disease secondary to Wegener's granulomatosis. This procedure is not associated with a higher risk than that facing other transplant patients. Although there are only limited data, triple maintenance immunosuppression in these patients is recommended for preventing rejection and relapses. Recurrence of the underlying disease after Tx seems to be rare, but careful monitoring of these patients is essential.

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