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Rituximab for remission induction in recurrent ANCA-associated glomerulonephritis postkidney transplant

Christine Murakami,[1] Pradeep Manoharan,[2] Naima Carter-Monroe[3] and Duvuru Geetha[1]

1 Department of Medicine, Division of Nephrology, Johns Hopkins University, Baltimore, MD, USA
2 Department of Emergency Medicine, Apollo clinic, Chennai, India
3 Department of Pathology, Johns Hopkins University, Baltimore, MD, USA

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Correspondence
Duvuru Geetha MD, MRCP (UK), Division of Nephrology, Johns Hopkins Bayview Medical Center, Johns Hopkins University, 301 Mason Lord Drive, Baltimore, MD 21224, USA.
Tel.: 410-550-2820;
fax: 410-550-7950;
e-mail: gduvura@jhmi.edu

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Summary

Kidney transplantation (KTX) is the treatment of choice for patients with end-stage renal disease (ESRD) due to ANCA-associated vasculitis (AAV). Recurrent ANCA-associated glomerulonephritis (GN) occurs after KTX and may adversely affect allograft survival. Cyclophosphamide (CYC) combined with glucocorticoids has been the cornerstone of treatment for recurrent GN. Rituximab (RTX), a B-cell-depleting monoclonal antibody, is approved for remission induction in AAV. We report the clinical presentation and outcomes of five KTX recipients treated with RTX for biopsy-confirmed recurrent GN. The median age at the time of KTX was 26 years (four Caucasian, three females). All patients were in remission with four being ANCA positive at time of KTX. Recurrent GN occurred at a median of 26 months post-KTX. All relapses were treated with RTX and glucocorticoids. Four patients achieved disease remission; the fifth patient was refractory to treatment with RTX and CYC. Follow-up biopsies (n = 3) showed resolution of active GN in two patients and persistent active GN in one patient. RTX is an alternative to CYC for remission induction in recurrent AAV-associated GN in KTX patients.

Introduction

ANCA-associated vasculitides (AAV) are rare small vessel vasculitides characterized by cycles of remission and relapse. These vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (eosinophilic granulomatosis with polyangiitis, EGPA). The introduction of therapy with glucocorticoids combined with cyclophosphamide (CYC) has changed the prognosis of AAV from an invariably fatal disease to a manageable chronic illness with an improved 5-year patient survival of 78% [1]. Renal involvement is common in AAV with 20–50% of patients having renal disease at presentation and 70–80% of patients developing renal involvement during the course of GPA and MPA. Despite the introduction of steroids and CYC, 20–30% of patients still develop end-stage renal disease (ESRD) [2–4].

As the mortality of patients with AAV continues to improve, our ability to address the consequences of ESRD in this patient population becomes paramount. Renal transplantation has been shown to improve survival and quality of life among patients with ESRD, and several studies have demonstrated that renal transplantation offers a survival benefit compared with maintenance dialysis [5,6]. Transplanted AAV patients have lower vasculitis relapse rates compared with those who remain on dialysis [7–11]. The patient and graft survival rates in transplanted AAV patients are comparable to other causes of ESRD [12,13]. However, vasculitis relapse can occur in as many as 50% of cases following renal transplantation and may adversely affect allograft outcome [14–23]. These relapses have been treated with CYC and corticosteroids, which has been the standard therapy for the past four decades. Although combination therapy with CYC and corticosteroids has been

effective in remission induction, the cost of remission is substantial with 42% of treated patients developing some form of treatment-related morbidity [24]. This fueled the search for alternative therapy. B cells have been implicated in the pathogenesis of AAV. Auto-antigen-specific B cells have been demonstrated at sites of inflammation, and B-cell activation has been correlated with disease activity in GPA. B cells are also responsible for the production of ANCA, which is involved in pathogenesis of AAV. In addition, the regulation of T cells is interdependent on B-cell function [25]. B-cell-targeted therapy using B-cell-depleting monoclonal antibody, rituximab (RTX), has been shown to be effective for remission induction in two large randomized trials [26,27]. The successful use of RTX for remission induction in recurrent AAV post-kidney transplantation (KTX) was first reported in two patients [28]. We report the clinical presentation, course, and outcomes of recurrent AAV affecting the allograft in five KTX recipients treated with RTX for remission induction.

Patients and methods

The study was approved by the Institutional Review Board. Records of all kidney transplant patients followed at the Johns Hopkins nephrology and vasculitis clinics were reviewed. Patients with a diagnosis of end-stage renal disease due to AAV were selected and classified as GPA or MPA based on Chapel Hill Consensus Conference Criteria [29]. KTX patients who had experienced a relapse of vasculitis in the renal allograft were included in this study. Relapse of vasculitis in the allograft was defined by the presence of hematuria (defined as more than five red blood cells in urine) or a rise in serum creatinine by 30% or biopsy-proven glomerulonephritis (GN). The following data were extracted: age at transplant, gender, race, donor type, disease type, ANCA type, and ANCA status at the time of transplant, details of induction and maintenance immunosuppression, episodes of rejection, best serum creatinine post-KTX following KTX surgery, timing of vasculitis relapse in relation to KTX, serum creatinine, urinalysis, inflammatory markers, ANCA status at the time of relapse and post-treatment with RTX, and adverse events were recorded. Additionally, we recorded time to remission as defined by a Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) [30] score of zero, details of repeat allograft biopsy, CD19 and CD20 counts post-RTX treatment when available. ANCA testing was carried out by standard indirect immunofluorescence assay on ethanol-fixed neutrophils for cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). An ANCA titer of less than 10 was considered to be negative for c-ANCA and p-ANCA (reference range 0–10). PR3 and MPO levels of <20 units were considered negative (reference range 0–20). B-cell depletion was defined as <10 $CD19^+$ B cells/μl.

Results

We identified 37 patients who underwent KTX for ESRD due to AAV between 1999 and 2012. Among these, seven patients experienced a renal relapse. Six patients underwent biopsy for cause, and a single patient underwent a protocol and follow-up biopsy for an episode of rejection that was treated prior to her vasculitis relapse. The first patient is a 47-year-old man with MPA involving the kidneys, who received a living-related renal transplant in 1999 after being on hemodialysis for 1 year and after his vasculitis was in remission for 1 year. ANCA status was unknown at the time of transplant. Two months post-transplant, he had a stable serum creatinine of 1.7 mg/dl but developed microscopic hematuria and his MPO-ANCA was positive. He had biopsy-proven pauci-immune necrotizing and crescentic GN. He was treated with steroids and oral CYC for 3 months and then switched to mycophenolate mofetil. His hematuria resolved at 4 weeks, and a repeat biopsy in 3 months showed resolution of GN. His serum creatinine at 1 year was 1.5 mg/dl and at 5 years was 1.6 mg/dl. The second patient is a 68-year-old woman with MPA involving the kidney who received a deceased donor renal transplant in 2000 after being on hemodialysis for 4 years and in clinical remission. She was ANCA negative prior to transplant. One month post-transplant, the serum creatinine increased from 1.4 mg/dl to 3.4 mg/dl and she had microscopic hematuria. Her MPO-ANCA was positive, and she has biopsy-proven pauci-immune necrotizing and crescentic GN. She was treated with steroids and 1500 mg twice daily of mycophenolate mofetil. Her serum creatinine improved to 1.3 mg/dl, hematuria resolved in 2 months, and she became ANCA negative. Her 1-year serum creatinine was 1.2 mg/dl and her 5-year serum creatinine was 1.3 mg/dl. The remaining five patients were treated with RTX, including the one patient reported from our institution in 2007, and we provide a detailed description of the clinical course of these five patients. The characteristics of these five patients at the time of KTX are shown in Table 1. The median age at the time of KTX was 26 years. The disease phenotype was MPA in three patients and GPA in two patients. The disease manifestations of vasculitis included pulmonary-renal syndrome in patient 1; renal limited vasculitis in patient 2; renal, lung, sinus, and joint involvement in patient 3; renal, lung, skin, and joint involvement in patient 4; and renal and joint involvement in patient 5. In four patients with detailed pretransplant information, the median interval between last documented active vasculitis and transplant was 32.5 months (range 16–40 months). All patients were in clinical remission of their vasculitis at the

Table 1. Baseline characteristics of patients with recurrent AAV.

Patient number	Age at TX (years)	Gender	Disease phenotype	ANCA type	ANCA status at the time of KTX	Induction therapy	Best creatinine post-KTX surgery (mg/dl)
1	23	F	MPA	P (MPO)	Negative	None	0.9
2	64	F	MPA	P(MPO)	Positive	ATG	0.6
3	26	M	GPA	C(PR3)	Positive	ATG	1
4	39	M	GPA	C (PR3)	Positive	ATG	1.2
5	19	F	MPA	P (MPO)	Positive	None	1.3

AAV, ANCA-associated vasculitides; TX, transplant; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; ATG, antithymocyte globulin; KTX, kidney transplantation.

time of KTX. In the pretransplant period, three patients were not on any immunosuppressive drugs, one patient was on azathioprine and one patient was on prednisone for remission maintenance of AAV. Four patients were ANCA positive at the time of KTX. Four patients received a live donor TX (Patient 2 was highly sensitized with a PRA of 94%, had donor-specific antibodies to HLA A24, HLA-CW4, HLA-DR11, and HLA-DR52, and received a HLA antibody incompatible KTX). and a single patient received a deceased donor KTX. Patient 2 received pretransplant intravenous immunoglobulin (IVIG) and plasmapheresis for desensitization. Three patients received induction therapy with antithymocyte globulin. All patients were discharged on a maintenance immunosuppressive regimen of prednisone, mycophenolate mofetil, and tacrolimus. The median follow-up was 59 months (range 10–92 months).

Allograft function

The best median serum creatinine post-KTX was 1.0 mg/dl (range: 0.6–1.3 mg/dl). The median 1-year serum creatinine was 1.5 mg/dl. Three patients experienced a total of three episodes of biopsy-proven allograft rejection, two of which preceded the vasculitis relapse date, while one of the episodes was concurrent with relapse (patients 2, 3, and 4). Patient 2 experienced humoral rejection with thrombotic microangiopathy 1 week post-transplant and was treated with splenectomy plasmapheresis, eculizumab and IVIG. Patient 3 experienced cell-mediated rejection 1 month post-transplant and was treated with glucocorticoids. Patient 4 experienced cell-mediated rejection concomitant with his recurrent GN and treated with antithymocyteglobulin. Two patients developed BK viremia on surveillance testing with no evidence of nephropathy (patients 2 and 5). Patient 2 developed BK viremia with 1600 copies/ml 3 months post-transplant. She did not undergo any immunosuppression reduction and had cleared her viremia at the time of her recurrent GN. Patient 5 developed BK viremia in the first 6 months and did not undergo any immunosuppressive dose reduction. She cleared her viremia 4 months preceding her recurrent GN.

Vasculitis relapse

The renal function and immunosuppression at the time of vasculitis relapse and post-treatment of relapse are outlined in Table 2. Five patients suffered a total of six renal relapses post-KTX. The median time to relapse was 26 months post-KTX. All patients presented with rise in serum creatinine and microscopic hematuria at the time of relapse. The median serum creatinine 1 month preceding relapse was 1.3 mg/dl (range 0.6–1.6 mg/dl). The median serum creati-

Table 2. Characteristics at time of vasculitis relapse.

Patient number	Time from KTX to relapse (months)	Organs involved	ANCA status at time of relapse	Serum creatinine 1 month preceding relapse (mg/dl)	Peak serum creatinine at time of relapse (mg/dl)	Treatment	Serum creatinine post-RTX (mg/dl)	Follow-up (months)	Serum creatinine at last follow-up (mg/dl)
1	72	Lung, kidney	Positive	0.9	2.1	P/RTX	1	85	1.0
2	6	kidney	Positive	0.6	0.9	P/RTX	0.9	10	0.9
3	13	Sinus, joints, kidney	Positive	1.6	2.2	P/RTX	2	59	2.0
4	46	Lung, skin, kidney	Positive	1.4	6.2	P/RTX/ATG	2.1	92	ESRD
5	26	Joints, kidney	Positive	1.3	1.7	P/RTX/CYC	ESRD	38	ESRD

P, prednisone; RTX, rituximab; ATG, antithymocyte globulin; CYC, cyclophosphamide; ESRD, end-stage renal disease; KTX, kidney transplantation.

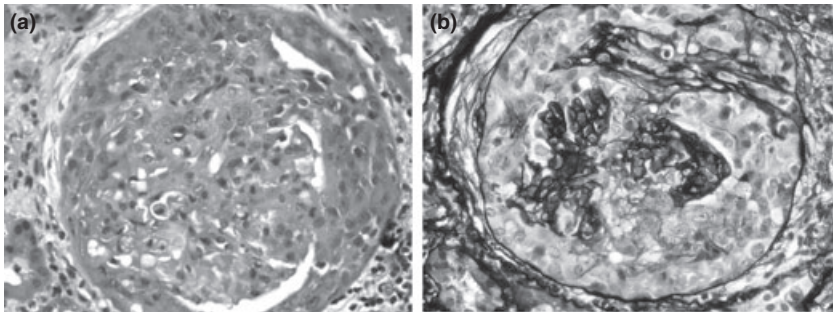

Figure 1 Biopsy from patient with focal necrotizing and crescentic glomerulonephritis consistent with recurrent granulomatosis with polyangiitis 13 months postrenal transplant demonstrating circumferential crescent formation on (A)H&E and (B)PAS-Methenamine silver stains (400× original magnification).

nine at the time of relapse was 2.1 mg/dl. Recurrent vasculitis in the allograft was biopsy proven in all five patients (Fig. 1). The allograft biopsy in all patients revealed necrotizing and crescentic GN on light microscopy. Patient 4 also had findings of cellular rejection. Four patients had extrarenal manifestations at the time of relapse. Among these four patients, all had migratory arthralgia, two patients had alveolar hemorrhage, one had sinusitis, and one had leukocytoclastic skin vasculitis. All patients were ANCA positive at the time of relapse. All but one patient had elevated erythrocyte sedimentation rate and C-reactive protein. The median peak serum creatinine at the time of relapse was 2.1 mg/dl. All patients were treated with glucocorticoids and RTX. RTX was used due to CYC intolerance in two patients (gastrointestinal and leukopenia in patient 3 and fever, rash, eosinophilia, and transaminitis in patient 4) and as primary therapy in the remaining three patients. The RTX dosing regimen was 375 mg/m^2 given intravenously once a week for 4 weeks in three patients (patients 1, 2 and 3) and 1000 mg RTX given intravenously for two doses given 2 weeks apart in two patients (patients 4 and 5). In addition, patient 4 with concurrent cellular rejection received antithymocyte globulin. The median follow-up post-treatment of relapse was 14 months (range: 9–79 months). Four patients achieved disease remission at a median of 3.5 months, while patient 5 had refractory vasculitis to RTX and CYC. Following treatment with RTX, the erythrocyte sedimentation rate and C-reactive protein normalized in all four patients, and the ANCA became negative in two patients and remained positive in the remaining three patients. All patients demonstrated B-cell depletion, and the median time to B-cell depletion was 1 month (range 3 weeks to 5 months). Among the five patients, four were continued on prednisone, mycophenolate mofetil, and tacrolimus for maintenance immunosuppression, while patient 4 was given chlorambucil for remission maintenance. Three patients had a follow-up allograft biopsy with resolution of active GN in two patients, while the third patient had persistent active GN (patient 5). Patient 5 with persistent active GN was treated with IV CYC, second course of RTX, and plasma exchange with no response and progressed to ESRD. Patient 4 had an episode of rejection and vasculitis relapse presenting as acute renal failure and alveolar hemorrhage 8 months post-RTX due to noncompliance with maintenance immunosuppressive drugs and required dialysis at presentation and reached ESRD. He was given plasmapheresis and glucocorticoids. This patient demonstrated B-cell reconstitution and a rise in ANCA titer at the time of his second relapse. He was not treated for recurrent vasculitis with RTX due to chronic changes on allograft biopsy as well as course complicated by CMV pneumonitis. The median serum creatinine post-treatment of relapse in the four patients that responded was 1.5 mg/dl. At the time of last follow-up, two patients reached ESRD: one due to refractory AAV and the other due to recurrent disease and allograft rejection in setting of medication noncompliance. Among the two patients that reached ESRD, one patient died of unknown cause 3 months after reaching ESRD. Patient 4 who received antithymocyte globulin and RTX experienced a bacterial pneumonia 10 days after first dose of RTX that responded to antibiotic therapy, the remaining four patients did not experience any adverse events.

Discussion

Rituximab, a chimeric anti-CD20 B-cell-depleting monoclonal antibody, has been approved for remission induction in AAV. The use of RTX for treatment of recurrent AAV in kidney transplant recipients is limited to case reports. We report the clinical course of recurrent AAV in five kidney transplant recipients treated with RTX. Four of the five patients achieved remission, while the fifth patient was refractory to both RTX and CYC.

ANCA-associated vasculitides are rare systemic vasculitides with an incidence of 20 per million per year. Despite

advances in diagnosis and treatment, renal morbidity is common with up to 20% of patients developing ESRD. KTX has been shown improve quality and quantity of life among patients with ESRD regardless on the etiology of ESRD and is the treatment of choice for AAV patients with ESRD. Transplanted vasculitis patients have graft and patient survival rates comparable to those observed in non-diabetic patients [14,31]. Transplanted vasculitis patients are at risk of having vasculitic relapses involving the allograft and extra-renal organs. The relapse rate ranges from 0.08 to 0.006 per patient per year with lower relapse rates reported with the use of modern immunosuppressive agents [13]. A recent literature review of 428 transplanted AAV patients showed that relapses occurred in 47 patients, corresponding to a relapse rate of 11%. Among 42 patients who had clinical information available about the relapse, recurrent GN was present in 38% of patients, whereas 48% of patients only had extra-renal recurrence [13]. A higher vasculitis relapse rate was reported in patients with GPA compared with MPA and in patients who are ANCA positive at the time of KTX compared with those who were ANCA negative at time of KTX [13].

Combination therapy with CYC and steroids has been standard therapy for recurrent vasculitis post-KTX [31]. This regimen is effective for remission induction in over 90% of patients [24,32]. However, the cost of achieving remission was substantial with 42% of patients developing some form of serious morbidity directly attributable to therapy; 46% of patients developed a serious infection, 57% became infertile, and 43% developed hemorrhagic cystitis. In addition, there was a 33-fold increased risk of bladder carcinoma and an 11-fold increased risk of lymphoma [24]. Modern treatment strategies have focused on minimizing CYC exposure or eliminating its use altogether. Both clinical and laboratory data support the role of B cells and ANCA in the pathogenesis of AAV [33]. B-cell-depleting therapy has therefore been tried as an alternative to CYC for remission induction in AAV. After initial promising data from smaller studies, two larger studies published simultaneously examined the use of RTX in the treatment of AAV. The larger of the two studies – RTX versus CYC for ANCA-associated vasculitis (RAVE) – was a multicenter, randomized double-blind, double-dummy, placebo-controlled noninferiority trial that evaluated the ability of RTX to induce remission in 197 subjects with severe AAV in comparison with CYC [26]. Remission was achieved in 64% and 53% of patients treated with RTX and CYC, respectively, and this result was significant for the noninferiority outcome. RTX, however, was more efficacious than CYC for inducing remission in relapsing disease. There was no difference in adverse events. The second study was the RITUXVAS (RTX versus CYC in ANCA-associated renal vasculitis) study, which randomized 44 subjects with AAV and renal involvement to RTX, 375 mg/m^2 given weekly for 4 weeks, and methylprednisolone with two doses of CYC versus CYC followed by azathioprine as maintenance therapy [34]. The rate of remission was similar in both arms (76 vs. 82%), and severe adverse events were comparable (42 vs. 36%) with 18% mortality in both groups. In April 2011, the FDA approved RTX for the treatment of AAV.

In the setting of KTX, RTX is used to treat antibody-mediated rejection, to reduce allo-antibodies prior to TX in ABO and HLA antibody incompatible transplants and to treat post-transplant lymphoproliferative disorder [35]. The first successful use of RTX for treatment of recurrent AAV post-KTX was reported in two patients in 2007 [28]. The present study extended the use of RTX for remission induction in recurrent AAV post-KTX to five patients. RTX was well tolerated without any adverse events in four patients and the fifth patients developed bacterial pneumonia 10 days post-RTX. However, this patient also received antithymocyte globulin. Four patients achieved disease remission, while the fifth patient had refractory disease and progressed to develop ESRD. Refractory vasculitis, defined as unchanged or increase in disease activity after 4 weeks of induction therapy, occurs in 5% of CYC-treated patients [36]. In the RAVE trial, refractory disease was present in 2% of RTX-treated patients. There is also evidence of pathogenic T cells in GPA, and this may play a role in refractory vasculitis and antithymocyte globulin has been used with success in these patients [37]. Other agents that have been tried in refractory disease include alemtuzumab [36].

We conclude that RTX is an alternative for CYC for remission induction in recurrent AAV in the allograft post-KTX.

Authorship

CM: participated in performance of research and writing of the article. PM: participated in data collection and analysis. NC-M: Participated in data collection and analysis, performance of research, and writing of the article. DG: participated in research design, performance of research, and writing of the article.

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