Efficacy of Combined Plasmapheresis and Intravenous Immunoglobulin Therapy in Kidney Transplant Patients With Chronic Antibody-mediated Rejection

Ebru Gok Oguz, Gulay Ulusal Okyay, Hadim Akoglu, Ozgur Merhametsiz, Tolga Yildirim, Basol Canbakan, Mehmet Deniz Aylı

Department of Nephrology, Diskapi Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey

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Introduction. Antibody-mediated rejections (AMRs) are critical clinical issues encountered in short- and long-term follow-up of kidney transplant patients. Whereas plasmapheresis is a mainstay treatment option in acute AMR cases, there is a paucity of data regarding its efficacy in management of chronic AMR. This report describes our experience addressing this issue.
Materials And Methods. We retrospectively investigated the data of 7 kidney transplant patients diagnosed with chronic AMR who were on 5 sessions of plasmapheresis (1 to 2 volume exchanges with fresh frozen plasma) on alternate days and 200 mg/kg of intravenous immunoglobulin after each session of plasmapheresis.
Results. At 6 months after the initiation of treatment, 6 patients experienced partially improved kidney function. One patient had no response and her kidney function progressively deteriorated.
Conclusions. Our preliminary results are encouraging for the combination of plasmapheresis and intravenous immunoglobulin as an adjunctive therapy for kidney transplant patients suffering from chronic AMR.

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INTRODUCTION

Antibody-mediated rejections (AMRs) are critical clinical conditions which could be encountered in short-term and long-term monitorization of kidney transplant patients. Acute AMR usually occurs early after transplantation with a sudden onset of elevation in serum creatinine levels. Plasmapheresis, an extracorporeal procedure in which the human plasma is separated from large molecules such as antibodies, immunocomplexes, cryoglobulins, and endotoxins, is one of the mainstay treatment modalities by which favorable outcomes could be reached in acute AMR cases.[1,2]

In the setting of chronic AMR, allograft function deteriorates in a slow and progressive manner. There have been some recommendations for its management such as augmentation of the doses of the immunosuppressive agents or administration of intravenous immunoglobulins.[3,4] However, a standardized therapy has not been established, yet. In recent years, novel strategies including plasmapheresis combined with antihumoral agents (intravenous immunoglobulins, rituximab, and bortezomib) have been tried in chronic AMR cases, with varied clinical outcomes.[5,6]

This report addresses our experience regarding the short-term efficacy of plasmapheresis and intravenous immunoglobulin combination in kidney transplant patients with chronic AMR.

MATERIALS AND METHODS

We investigated our kidney transplant patients

who had allograft biopsy between January 2013 and January 2015 at our institute. A total of 26 kidney transplant patients had undergone allograft biopsy. Their histopathological diagnoses were as follows: 7 patients were diagnosed with chronic AMR; 6 patients, chronic allograft injury; 4 patients, acute cellular rejection; 3 patients, acute AMR; 3 patients, calcineurine inhibitor toxicity; 2 patients, BK polyoma virus nephropathy; and 1 patient, acute tubular necrosis.

Chronic AMR was diagnosed in 7 patients who had serologic evidence of circulating donor-specific alloantibodies (DSA; examined by luminex assay) as well as histologic evidence of diffuse deposition of C4d (a degradation product of complement pathway) and chronic tissue injury on allograft biopsy speciemens (Table 1). After transplantation, all of the patients were on triple immunosuppressive therapy including prednisolone, a calcineurin inhibitor (cyclosporine or tacrolimus), and an antimetabolite agent (mycophenolate sodium or azathioprine).

After the diagnosis of chronic AMR, prednisolone and antimetabolites were maintained; cyclosporine was switched to tacrolimus in patients 2, 4 and 5; azathioprine was switched to mycophenolate sodium in patients 2 and 5. Tacrolimus was adjusted to keep through a plasma concentration in levels between 4 ng/mL and 8 ng/mL. Then, each patient received 5 sessions of plasmapheresis under fresh frozen plasma every other day. Plasma volume was estimated using the following formula:

0.065 × body weight (kg) × (1 - hematocrit)

The volume exchange was titrated between 1 and 2 plasma volumes, depending on patient tolerance and clinical response. The patients were also given 200 mg/kg of intravenous immunoglobulin after each session of plasmapheresis.

Kidney function was determined by serum creatinine value, protein excretion rate measured in 24-hour urine samples, and glomerular filtration rate estimated using the Modified Diet in Renal Disease equation at baseline, at the time of allograft biopsy, and after 6 months of rejection therapy.[7]

RESULTS

The demographic characteristics of the patients diagnosed with chronic AMR are presented in Table 1. Their primary kidney diseases were unknown and all had their first transplantation. All had living related

Table 1. Clinical Characteristics of Kidney Transplant Patients With Chronic Antibody-mediated Rejection (AMR)

Patient	Sex	Age, y	Hemodialysis Duration	HLA Mismatch	History of Acute Rejection	Chronic AMR Diagnosis After Transplant, y	Serum Creatinine, mg/dL			Golmerular Filtration Rate, mL/min/1.73 m^2			Proteinuria, mg/d		
							Baseline	At Biopsy	After 6 Months*	Baseline	At Biopsy	After 6 Months*	Baseline	At Biopsy	After 6 Months*
1	Male	32	1 y	2	No	14	1.3	3.0	1.6	67.99	25.90	53.93	14	1485	1514
2	Male	30	2 y	2	No	12	2.0	4.1	2.1	41.91	18.30	39.61	2.3	2214	1994
3	Female	40	3 y	3	Yes	11	2.5	5.2	3.0	22.67	9.74	18.37	4.3	1852	1900
4	Male	48	2 mo	2	No	10	2.2	4.8	2.4	34.12	13.87	30.86	3.26	3278	1790
5	Female	42	8 mo	2	No	16	2.2	4.2	2.5	26.02	12.34	22.45	3.57	4700	2580
6	Female	38	4 mo	4	Yes	1.5	1.3	12.9	3.9	48.72	3.45	13.70	35	2950	2800
7	Male	40	8 y	2	No	15	1.5	3.7	2.0	55.09	19.44	39.53	15.56	2900	2840

*Refers to values after 6 months of rejection therapy.

donors with the exception of patient 6 who had living unrelated donor. None of them had attended their regular follow-up visits; moreover, patients 3 and 6 had withheld their immunosupressive agents for a period of time. There were no history of accompanying diseases or medication use other than immunosuppressive drugs.

Laboratory results showed impaired kidney function and calcineurin inhibitor concentrations lower than the target blood levels (Table 2). Urinary tract infection was not found in any of the patients. Renal ultrasonographic examinations revealed no obstructive lesions. Doppler ultrasonographies showed normal filling of the renal arteries and veins. Findings of chronic tissue injury were transplant glomerulopathy (all patients), tubulitis with variable degrees (patients 1, 2, 5, 7 at baseline; patients 3, 4, 6 at the time of biopsy), tubular atrophy (all patients), interstitial infiltration (all patients), interstitial fibrosis (all patients), local (patients 1 to 6) or diffuse peritubular capillaritis (patient 7), and fibrin thrombus (patient 3). The histopathological characteristics of the allograft biopsies are presented in Table 3.

After 6 months of rejection therapy, 6 patients experienced a considerable improvement in their serum creatinine and estimated glomerular filtration rates; patients 4 and 5 had relatively lower daily protein excretion rates, and the rest had stabilized values. Patient 6 had no response and her allograft function gradually deteriorated (Table 1). After 12 months, this patient started maintenance hemodialysis therapy.

DISCUSSION

Antibody-mediated rejections are particularly important clinical conditions which could eventually lead to allograft failure in kidney transplant patients.[1] The American Aphaeresis Association advises the usage of plasmapheresis for patients with kidney allograft rejections in combination with immunosuppressive therapy, since the quick clearance of antibodies through plasmapheresis increases de novo antibody synthesis.[8]

In the setting of acute AMR, various treatment options could achieve protection of allograft function in approximately 80% of the cases.[9] In acute AMR patients, plasmapheresis is used either as soon as the acute AMR is diagnosed or when corticosteroids and antithymocyte globulin fail to produce a sufficient clinical response.[1] On the other hand, chronic AMR was manifested in 9.3% of unselected indication biopsies by 10 years and has a poor prognosis.[10] The risk of graft loss increases by

Table 2. Immunsuppressive regimens and calcineurin inhibitor doses of patients with chronic antibody mediated rejection.

Patient	Prednisolone, mg/d	Cyclosporine		Tacrolimus		Mycophenolate Sodium, mg/d	Azathioprine, mg/d
		Dose, mg/d	Serum Level, ng/mL*	Dose, mg/d	Serum Level, ng/mL*		
1	5	…	…	2	3	1440	…
2	5	100	240	…	…	…	100
3	5	…	…	2	1	1080	…
4	5	100	220	…	…	1080	…
5	5	100	248	…	…	…	100
6	5	…	…	2	0.5	720	…
7	5	…	…	6	3.2	1440	…

*Serum level at the 2nd hour.

Table 3. Histopathology of Allograft Biopsies

Patient	C4d Positivity	Glomerulopathy	Tubulitis	Tubular Atrophy	Peritubular Capillaritis	Interstitial Infiltration	Interstitial Fibrosis	Fibrin Thrombus	Banff Classification*
1	Diffuse	+	t1	+	Focal	+	+	-	I/III
2	Diffuse	+	t1	+	Focal	+	+	-	II/III
3	Diffuse	+	t2	+	Focal	+	+	+	II/III
4	Diffuse	+	t2	+	Focal	+	+	-	II/III
5	Diffuse	+	t1	+	Focal	+	+	-	II/III
6	Diffuse	+	t2	+	Focal	+	+	-	II/III
7	Diffuse	+	t1	+	Diffuse	+	+	-	II/III

*Banff '07 classification

about 6-fold.[11] One-year and 5-year graft survival rates were 54 % and 8 %, respectively.[12] A few studies showed clinical and functional stabilization with combination of intravenous immunoglobulin and rituximab in chronic AMR cases.[4,13] Fehr and colleagues reported improvement in their 4 of 5 chronic AMR cases[4]; while Billing and coworkers defined stabilization of kidney functions in their 4 of 6 cases.[13] The most important disadvantage of rituximab therapy is increased risk of pneumocystis jiroveci pnemonia.[14,15]

There is paucity of dataregarding the efficacy of plasmapheresis in management of patients suffering from chronic AMR,[5,6] which is likely the result of an indolent alloimmune response that could result in transplant glomerulopathy and microcirculatory inflammation. Güngör and colleagues[5] performed 4 sessions of plasmapheresis for 4 patients and 7 sessions of double-filtration plasmapheresis for 1 patient, all of whom were suffering from chronic AMR. They reported a good clinical outcome only in 1 patient. Kim and colleagues[6] presented their results with anti-humoral combination therapies in 9 kidney transplant patients. They used 3 distinct regimens including rituximab plus high dose intravenous immunoglobulin; rituximab, bortezomib, plus high-dose intravenous immunoglobulin; and rituximab, bortezomib, low dose intravenous immunoglobulin, plus plasmapheresis. They declared that 6 of their patients had at least stabilized allograft functions, but 3 patients showed detorioration after the treatment with one of these protocols. In the present study, 6 of 7 patients showed partially improved kidney function at 6 months of rejection therapy compared to the values at time of allograft biopsy. Two patients had partially improved protein excretion rates and the others had stabilized values at the 6th month after treatment with plasmapheresis plus intravenous immunoglobulin. We thought that plasmapheresis reduced the produced alloantibodies in the circulation and intravenous immunoglobulin prevented the production of de novo alloantibodies; thus, progression of kidney injury stopped in these cases. However, patient 6 did not have an improvement in her kidney function and lost her allograft in 12 months. We considered that there were some particular factors increasing her immunological risk and contributing to poor prognosis. First of all, her kidney donor was an unrelated person with 4 human leukocyte antigen mismatch. Second, she had had an acute humoral rejection episode on the 6th month of transplantation and had taken pulse corticosteroid therapy combined with plasmapheresis. Moreover, she had never come to control visits timely and she had witheld her immunosupressive drugs for 1 month at the time of presentation with impaired kidney function.

Although we observed favorable outcomes in the vast majority of our patients, there are indefinitive points for management of patients with chronic AMR, one of which is the type of plasmapheresis. We performed plasma exchange therapies on alternate days with 1 to 2 volume exchanges with fresh frozen plasma. The duration of therapy is another aspect. We performed 5 sessions of plasma exchange. Monitoring of kidney function and DSA titers could give information about the effectiveness and continuation of the plasmapheresis. However, we could not measure the DSA titers after the treatment.

According to the results of the Efficacy Limiting Toxicity Elimination-Symphony Study,[16] calcineurin inhibitors have been used at lower doses in clinical practice. Hence, the frequency of allograft losses due to rejection has increased.[17] Supportingly, in the present study, just 3 patients (11.6%) had calcineurin toxicity; while 7 patients (26.9%) had chronic AMR. Therefore, monitorization of allograft function and plasma levels of immunsupressive drugs are of critical importance in kidney transplant patients even if they do not have any complaints. Calcineurin concentrations, adherence to treatment, intervals between follow-up visits, the donor type, and the number of human leucocyte antigen mismatchs are the factors which may affect the responses to plasmapheresis in chronic AMR cases.

CONCLUSIONS

Chronic AMR is a serious complication of kidney transplantation and has a negative impact on graft survival. Our results are encouraging for use of plasmapheresis as an adjunctive therapy for patients suffering from chronic AMR. However, further studies with larger number of patients and prospective designs are needed to confirm the presented results.

CONFLICTS OF INTEREST

None declared.

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Correspondence to:
Ebru Gok Oguz, MD
Department of Nephrology, Ankara Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey
Tel: +90 506 314 8406
Fax: +90 312 311 6351
E-mail: ebrugokoguz@hotmail.com

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