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Research Article

Three-Year Outcome of Kidney Transplant Recipients with Donor Specific Anti-HLA Antibody (DSA) and Positive C4d in Graft Tissue

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Abstract

Background: Donor specific anti-HLA antibody (DSA) in sera and positive C4d in graft tissue have been reported as a poor prognostic indicator for kidney graft outcome. However, management of this condition has not been established.

Methods: We examined the role of treatment with plasmapheresis, followed by intravenous immunoglobulin (ivIG), and rituximab in 23 renal allograft recipients presenting with DSA and/or positive C4d. Graft function was monitored for 3 years after the treatment.

Results: Among 8 patients who received the treatment within the first year of kidney transplant, improvement in graft function was noted in 4 (50%) subjects, 3 (37.5%) showed no change, and only one (12.5%) had worsening in graft function, whereas among 13 patients who received the treatment after the first transplant year, 9 (69.2%) showed no change, 4 (30.8%) had worsening of graft function, and none showed improvement (p=0.018). Among 10 patients with graft dysfunction; with s-Cr > 20% above nadir at the time of the treatment, 3 (30%) showed improvement, 3 (30%) showed no change, 4 (40%) had further worsening of graft function, whereas majority of subjects (9 among 11) with stable graft function at the time of treatment showed no change on follow-up.

Conclusion: We suggest that, in patients manifesting DSA and/or C4d, a series of treatment including plasmapheresis, ivIG, and rituximab may play a beneficial role in long-term renal graft outcome if it is administered within the first year of transplant, especially in the case of graft dysfunction.

Keywords: Antibody mediated rejection; Donor specific antibody; Plasmapheresis; Immunoglobulin; Rituximab

Introduction

Prevention and treatment of rejection is the mainstay of managementin recipients of a renal allograft. Recently, with introduction of new agents to the armamentarium of immunosuppressive regimen, the rate of acute cellular rejection (ACR) has markedly decreased [1-3]. However, the detrimental effects of acute antibody-mediated rejection (AMR) have been increasingly recognized [4, 5]. Plasmapheresis, intravenous immunoglobulin (ivIG), rituximab, splenectomy, bortezomib and eclizumab as well

as increased maintenance immunosuppression have used as treatment or prevention of acute AMR [6-12]. Moreover, appearance of donor specific anti-HLA antibody (DSA) in circulation and positive Cd4 staining in the graft tissues have been reported as a poor prognostic indicator for long term graft survival, which is likely associated with chronic AMR [13-17]. However, management of this condition has not been standardized. We questioned whether a series of plasmapheresis, ivIG, and rituximab would have a beneficial role in the management of the patients manifesting such antibody mediated changes and improve long-term functional outcome of the renal allografts.

Materials and Methods

In this pilot trial, subjects were 23 adult recipients of a renal allograft who had presented with DSA in the blood and/or positive C4d staining in graft biopsy tissues and received a series of treatments including plasmapheresis, ivIG and rituximab.The treatment comprised plasmapheresis replacing one plasma volume with 5 % albumin on days 1, 2, 3, 5, and 7, followed by ivIG in an amount of 2 gm/kg at a maximum of 140 gm on day 8, and Rituximab 375 mg/m^2 on day 10. Intravenous methylprednisolone 500 mg, oral acetaminophen 650 mg, and intravenous diphenhydramine 50 mg were administered prior to ivIG and rituximab. A repeat graft biopsy was performed around day 14. Renal graft function was followed by serum creatinine concentration (s-Cr) for 3 years after the series of treatment. Two subjects had graft failure, 7 days and 30 days after the treatment. They were excluded from analysis of long-term outcome. Controls were 13 recipients of a renal allograft who had DSA detected, but did not receive the series of treatments. Controls were monitored for renal graft function for up to 3 years. One patient in control group lost the graft 3 days after donor specific antibodies were detected and was excluded from the analysis. Twenty-one subjects and 12 controls were analyzed for functional outcome of the graft on the last follow-up at a median of 30 and 33 months, respectively. All 21 subjects had graft biopsy prior to the treatment. Histologic grading of the graft biopsy samples was performed following the Banff 07 Classification of Renal Allograft Pathology [18]. Acute cellular rejection was treated with intravenous methylprednisolone or anti-thymocyte globulin raised in rabbits (Thymoglobulin). HLA typing was determined by LABType (One Lambda Inc. Canoga Park, California), a reverse sequence specific oligonucleotide probe method. DSA was determined by LABScreen PRA and Single Antigen bead (One Lambda Inc.). DSA was considered positive when mean fluorescent intensity (MFI) was above 1000. S-Cr on the first day of the series of treatments, prior to initiation of the treatment, was treated as baseline. If s-Cr at the time of last follow-up was > 20% above or > 20% below the baseline value, the functional outcome of the graft was defined as worse or better, respectively. The others were defined no change. Anti-HLA antibodies for DSA were monitored at variable intervals, weekly to yearly depending on the stage after transplant and assessed risk of AMR in individual patients.The significance of differences in characteristics of patients and transplants between the subject and control groups was determined using Student‘s unpaired t-test or Chi-square analysis. Analyses were performed to compare the functional outcome of subjects with the controls by Pearson Chi-square analysis, using variables including timing of the treatment post-transplant, graft function, presence of ACR, severity of Interstitial Fibrosis/Tubular Atrophy (IF/TA) of the graft tissue, duration of DSA, and severity of peritubular capillary inflammation (PTC) in the tissue at the time of treatment. All statistical analyses were performed using software SPSS 21 or SAS 9.1.3.

Results

Patient and Transplant Characteristics

Twenty-three recipients of a renal allograft who manifested antibody mediated changes by DSA in the blood and/or C4d positivity in graft tissues received a series of treatment with five sessions of plasmapheresis followed by ivIG and rituximab. As shown in (Table 1).

	Subjects	%	Controls	%	P
Number of Patients	23		13		
Age; mean ± SD	52 ± 17		49 ± 19		0.6651
Gender; Female/Male	6/17	*74*	4/9	*69*	0.597
Ethnicity; Caucasian/African American	22/1	*96*	12/1	*92*	1
Cause of ESRD					0.083
Diabetes	9	*39*	1	*8*	
Hypertension	1	*4*	5	*38*	
Glomerulonephritis	7	*30*	3	*23*	

Interstitial Nephritis	1	*4*	2	*15*	
Urinary tract reflux disease	2	*9*	1	*8*	
Congenital kidney disease	2	*9*	0	*0*	
Polycystic kidney disease	0	*0*	1	*8*	
Unknown	1	*4*	0	*0*	
Graft Failure	3	*13*	1	*8*	
Donor Type					0.3246
Living related	3	*13*	2	*15*	
living unrelated	9	*39*	2	*15*	
deceased	11	*48*	9	*69*	
Donor Age; mean ± SD	38 ± 14		31 ± 17		0.2688
Cold Ischemic Time (minutes); mean ± SD	438 ± 34		603 ± 21		0.2758
Serum Creatinine ≥ 1.5 mg/dl on post-transplant day 7	8	*35*	8	*62*	0.1486
Induction Immunosuppression	14	*61*	8	*62*	0.1841
Thymoglobulin	10	*43*	3	*23*	
Alemtuzumab	4	*17*	4	*31*	
Daclizumab	0	*0*	1	*8*	
Maintenance Immunosupression					0.192
FK, M, Pred	13	*57*	5	*38*	
FK, M	6	*26*	4	*31*	
FK, Pred	1	*4*	0	*0*	
FK	2	*9*	0	*0*	
Cyclosporine, M, Pred	1	*4*	0	*0*	
FK, Sirolimus, Pred			1	*8*	
M, Sirolimus			1	*8*	
Rapamycin			2	*15*	
Days after Transplant; mean ± SD	1333 ± 1345		1331 ± 791		0.9946
median	1043		980		
range	6-5110		170-2675		
Graft dysfunction; s-Cr >20% above recent nadir value	12	*52*	2	*15*	0.03

FK, M, Pred denote tacrolimus, Mycophenolate mofetil or Myfortic acid, prednisone, respectively.

s-Cr indicates serum creatinine concentration.

Percentage is expressed in Italic letters.

Table 1: Characteristics of patients and transplants

There were no significant differences in baseline characteristics between the subjects and controls. The one exception was graft dysfunction which occurred in 52% of subjects as compared to 15% of controls. The mean age of subjects was 52 years which was not significantly different from controls. There were more male patients than female in both subject and control groups. Caucasians were the major ethnicity represented, reflecting the general population in central Pennsylvania. Diabetes and hypertension were the main causes of end stage of renal disease without significant difference between the groups. Three among 23 subjects (13%) and 1 among 13 controls (8%) had a repeat kidney transplant due to previous graft failure. Eleven among 23 subjects (48%) and 9 among 13 controls (69%) received kidney transplant from a deceased donor. Mean donor age was 38 years in subjects and 31 years in controls without significant statistical difference. Mean cold ischemic time was 438 and 603 minutes in subjects and controls, respectively, without significant difference. Eight among 23 subjects (35%) and 8 among 13 controls (62%) had slow or delayed early graft function defined as serum creatinine concentration (s-Cr)≥1.5 mg/dl on post-transplant day 7. The Majority of patients received induction immunosuppression with Thymoglobulin, Alemtuzumab or Daclizumab; 61% in subjects and 62% in controls. At the initiation of the series of treatments in subjects and at the first detection of DSA in controls, the median days post-transplant was 1043 (range: 6-5110) and 980 (range: 170-2675), respectively without significant difference. Among the 23 subjects, at the time of initiation of the treatment, 12 had graft dysfunction judged by more than 20% increase in s-Cr above the nadir value of the previous 3 months. Two of these subjects developed graft failure within a month of follow-up. Only two among 13 controls had graft dysfunction using the same criteria. One of the controls had graft failure within a month. Those who developed graft failure within the first month of follow-up were excluded from analysis.

Functional outcome

Among 21 subjects analyzed for functional outcome, 4 (19%) had improved, 12 (57%) showed no change in graft function at the time of last follow-up, and 5 (24%) worsened graft function. In 2 subjects, graft failure occurred at 9 months and 1 year. Among 12 patients analyzed in the control group, 10 (83%) showed no change and 2 (17%) had worsening of the graft function. The difference in functional outcome between the subject and control groups did not reach statistical difference. Of note, no subject or control developed acute AMR during the 3-year follow-up period.

Effect of graft dysfunction and time post-transplant

Among the 21 subjects, 10 had had graft dysfunction prior to the initiation of the treatment. Among the 10 patients with graft dysfunction, 3 (30%) showed improvement, 3 (30%) showed no change, 4 (40%) had further worsening of graft function, whereasmajority of subjects (9 among 11) with stable graft function at the time of treatment showed no change on the last follow-up (Table 2, upper panel).

	with Graft dysfunction		without Graft dysfunction	
N	10	%	11	%
No Change	3	30	9	82
Better	3	30	1	9
Worse	4	40	1	9

Graft dysfunction is defined as s-Cr above baseline by > 20%.

	Within 1 year		After 1 year		P
N	8	%	13	%	0.018
No Change	3	37.5	9	69.2	
Better	4	50	0	0	
Worse	1	12.5	4	30.8	

Table 2: Functional outcome of renal allografts in subjects with and without graft dysfunction at the initiation of treatment; Functional outcome of renal allografts depending on time post-transplant

Eight patients in the subject group received the treatment within the first year of transplant and 13 patients after the first year. Among the eight patients who received the treatment within the first year, improvement of the graft function was noted in 4 (50%), 3 (37.5%) showed no change in graft function, and worsening in only one (12.5%). In contrast, among 13 patients who received the treatment after the first year of transplant, 9 (69.2%) showed no change, none had improvement, and 4 (30.8%) had worsening in graft function (p=0.018), suggesting a beneficial effect of treatment on the long-term graft functional outcome when it was administered within the first year of transplant (Table 2, lower panel). However, the positive effect was not observed when the treatment was given more than a year after transplant, compared to the control group.

Effect of Acute Cellular Rejection (ACR)

Only one among 4 subjects who showed the recovery of graft function had coexisting ACR at the time of the treatment, whereas 4 of 5 subjects who showed worsening of graft function had coexisting ACR. Among 21 subjects, 13 had coexisting ACR at the time of the treatment, 11 developed ACR within the first year after treatment, and 8 had ACR both at the time of treatment and later during the first year of follow-up. Graft functional outcome was compared between those with and without ACR (Table 3, upper panel).

	with ACR		without ACR	
N	13	%	8	%
No Change	8	61.5	4	50
Better	1		3	37.5
Worse	4	30.8	1	12.5

	IF/TA 0 and 1 (<25%)		IF/TA 2 and 3 (> 25%)	
N	17	%	4	%
No Change	10	59	2	50
Better	4	23	0	
Worse	3	18	2	50

Table 3: Functional outcome of renal allografts in subjects with or without coexisting acute cellular rejection (ACR) at the time of treatment; Functional outcome of renal allografts in subjects depending on the severity of interstitial fibrosis and tubular atrophy (IF/TA).

The presence of coexisting ACR at the time of the treatment tended to adversely affect the functional outcome.

Effect of Interstitial Fibrosis/Tubular Atrophy (IF/TA)

Among the 21 analyzed subjects, 17 had mild degree of IF/TA; grade 0 or 1 (< 25 % involvement of renal parenchyma) and 4 had IF/TA grade 2 or 3 (> 25 % involvement of renal parenchyma) at the time of treatment. IF/TA grade 0 and 1 tended to be associated with better functional outcome than IF/TA 2 and 3 (Table 3, lower panel).

Effect of Donor specific anti-HLA antibody (DSA)

As shown in Tables 4 and 5, 11 of the 21 subjects had detectable DSA. Of these, 6 had newly detected DSA on routine monitoring on10 to 1186 (median 666) days post-transplant. After detection, four underwent the series of treatments 7 to 12 days (7, 8, 8, 12) later and two underwent the treatment 51 and 368 days after detection. The other 5 patients had DSA of unknown duration detected 2001 to 4750 days post-transplant; median 2696 days.All except one underwent the treatment 3 to 21 days (3, 4, 14, 21, 360 days) after detection. The effect of the treatment on functional outcome of the graft was not significantly different in patient with newly detected DSA from those with DSA of unknown duration (Table 4, upper panel).

	New	Old or Unknown duration		
N	6	%	5	%
No Change	3	50	4	80
Better	1	17		
Worse	2	33	1	20

	0 and 1		2 and 3	
N	15	%	6	%
No Change	8	53	4	67
Better	4	27	0	0
Worse	3	20	2	33

ptc 0; no significant cortical ptc, or < 10% of ptc with inflammation

ptc 1; ≥ 10% of cortical peritubular capillaries with capillaritis, with max 3 to 4 luminal inflammatory cells

ptc 2; ≥ 10% of cortical peritubular capillaries with capillaritis, with max 5 to 10 luminal inflammatory cells

ptc 3; ≥ 10% of cortical peritubular capillaries with capillaritis, with max > 10 luminal inflammatory cells

Table 4: Functional outcome of renal allografts in subjects depending on the nature of donor specific anti-HLA antibody (DSA); Functional outcome of renal allografts in subjects depending on the grade of peritubular capillary (PTC) inflammation

Among the 11 DSA positive subjects, DSA was detected transiently for 10 to 398 days in 7 subjects while being monitored and 4 subjects had persistent antibodies for at least 26 to 554 days. No significant difference in functional outcome was found in the 7 subjects with transient DSA (4 with no change, 1 better, 2 worse) compared to the 4 subjects with persistent DSA (3 with no change, 1 worse) in the treatment group.

Effect of positive C4d staining in graft tissues

As shown in Table 5, among 21 subjects, all except one had positive C4d staining in the graft tissues. Nineteen of the 20 subjects who had positive C4d staining prior to the treatment underwent a repeat biopsy median 17 days (range 14-98 days) later, after the treatment. Majority; Thirteen (68%) of them showed negative staining for C4d and only 6 (32%) showed persistently positive staining for C4d on the repeat biopsy. The subject with negative C4 staining at the time of the treatment showed persistent negative staining on a repeat biopsy 14 days later.

Effect of peritubular capillary inflammation (PTC)

Among the 21 subjects, 14 had no peritubular capillary inflammation (PTC 0); one, PTC 1; four, PTC 2; two, PTC 3 in graft biopsy tissues at the time of treatment. None of 7 subjects with PTC 1, 2, or 3 had improved graft function after the treatment; function worsened in two and was unchanged in five. Among 7 subjects with PTC 1,2, or 3, three had graft dysfunction at the time of treatment and four had stable graft function. Graft functional outcome tended to be better in subjects with a mild degree of inflammation (PTC 0 and 1) compared to PTC 2 and 3 (Table 5 and Table 4 lower panel).

			Baselines findings at the initiation of the treatment								Repeat biopsy				Last follow-up			DSA	
Subjects	Nadir s-Cr during recent 3 months prior to the treatment	Post-transplant days of first DSA detection	DSA, Class I	DSA, Class II	C4d	PTC	ACR, coexisting	IF/TA, grade	Post-transplant Days	s-Cr	Days after pre treatment biopsy	C4d	PTC	ACR within 1yr after treatment	months after treatment	s-Cr	graft functional outcome	Transient vs. Persistent	Duration of DSA detected, days
1	2.3				Positive	1	YES	3	1201	2.21	98	Negative	2	YES	36	2.49	No change		
2	1.87				Positive	0	NO	0	8	2	14	Negative	0	NO	30	1.5	Better		
3	3.45*				Positive	0	NO	0	6	1.24	15	Negative	0	YES	36	1	No change		
4	0.8	931	A1	none	Positive	2	YES	1	982	**1.33**	**			**	36	1.2	No change	T	33
5	1.81	2521	none	DR53, DQA103	Positive	3	YES	1	2525	1.67	19	Positive	2	YES	36	1.5	No change	P	333
6	1.02	10	B8	none	Negative	0	NO	0	17	**1.78**	14	Negative	0	NO	36	1.18	Better	T	10
7	6.03	Graft failure within a month	Positive						3266	**2.99**	21	Positive							
8	1.6	2696	A29	DPA102	Positive	2	YES	2	2717	1.38	15	Negative	0	NO	30	1.7	Worse	P	34
9	1.9	Graft failure within a month	Positive						2548	**7.18**									
10	1.09				Positive	0	NO	0	13	**1.94**	18	Positive	0	YES	18	2.6	Worse		
11	1.54	4750	B7	DR13, DQ6	Positive	3	NO	1	5110	1.5	38	Positive	2	NO	36	1.21	No change	P	554

12	1.3	400	none	DQ6	Positive	0	YES	1	768	1.29	16	Negative	2	YES	18	1.45	No change	T	86
13	1.28				Positive	0	NO	0	7	**3.16**	87	Negative	0	YES	30	1.32	Better		
14	2.3	1031	none	DQ6	Positive	2	YES	2	1043	**2.82**	15	Negative	1	YES	12	4.33	Worse	T	11
15	1.41				Positive	0	YES	1	2506	**4.08**	28	Positive	0	YES	12	8.57	Worse		
16	1.66				Positive	0	YES	0	31	**2.01**	16	Negative	0	YES	36	1.5	Better		
17	1.3				Positive	0	YES	1	211	1.5	22	Negative	0	YES	30	1.45	No change		
18	1.3	1186	none	DQ7	Positive	0	YES	1	1194	**1.76**	15	Positive	0	NO	36	2.63	Worse	T	398
19	0.75				Positive	0	NO	0	6	0.75	22	Negative	0	NO	36	0.9	No change		
20	1.42				Positive	0	NO	0	1305	**1.87**	18	Negative	0	NO	24	1.6	No change		
21	1.45	2001	none	DQ4	Positive	0	YES	1	2004	1.38	17	Negative	0	YES	36	1.31	No change	T	58
22	1.6	2816	none	DC2, DQ7	Positive	2	YES	2	2830	**2.01**	14	Positive	0	NO	30	1.84	No change	P	26
23	1.1	397	A2	DQA103	Positive	0	YES	1	405	1.31	14	Negative	1	NO	18	1.05	No change	T	182

DSA; donor specific anti-HLA antibody, PTC; scoring of peritubular capillary inflammation, ACR; acute cellular rejection, IF/TA; interstitial fibrosis and tubular atrophy grade, s-Cr; serum creatinine concentration

*Post-transplant delayed graft function in recovery, **no repeat biopsy

DSA in bold letter indicates newly detected on weekly to yearly monitoring after transplant, s-Cr value in bold letter indicates graft dysfunction; s-Cr> 20% above nadir value. Graft functional outcome is defined worse or better, if s-Cr at the time of last follow-up is >20% above or >20% below of the base line value, respectively.

T and P denote transient and presistent, respectively.

Transient; DSA became undetected while monitoring vs Persistent; DSA deteted until the last check.

Table 5: Charateristics of recipients of a renal allograft who received a series of five sessions of plasmapheresis, intavenous immunoglobulin and rituximab

Discussion

Newly formed circulating DSA and C4d positivity in renal allografts have been reported as poor prognostic indicators for long-term renal allograft survival [13-17, 30-32]. Previously, ivIG and Rituximab have been used to manage chronic AMR with variable response [19-22]. However, standard management of the condition has not been established. In this pilot study, appearance of DSA in the blood and/or positive Cd4 staining in graft tissues were considered manifestation of antibody mediated immune response, which could potentially culminate in antibody mediated rejection and worsen graft functional outcome. A series of treatments comprising five sessions of plasmapheresis followed by ivIG and rituximab was administered in 23 recipients of a renal allograft who manifested such antibody mediated changes. Approximately half of the subjects did not show a significant change in graft function in up to 3 years of follow-up. However, our analysis suggested that the treatment had a significant beneficial effect on long-term graft functional outcome when administered within the first year of transplant compared to the treatment given more than a year after transplant. In other words, when the treatment is given more than a year after transplant, no beneficial effect on the graft outcome was noted. The findings also suggested that the treatment did not improve graft functional outcome in the patients who had kidney transplant more than a year ago compared to untreated controls.

Acute AMR is a form of renal allograft rejection that typically occurs a few weeks after transplantation and is associated with circulating antibodies to donor HLA class I, class II, or non-MHC antigens on endothelium and portends poor prognosis [5]. It has been suggested that assessment of C4d in peritubular capillaries is a useful adjunct in the diagnosis of acute AMR as it dis-

tinguishes acute AMR from ACR in renal transplant biopsies [5]. Furthermore, it has been reported that C4d positivity in kidney graft tissues is associated with inferior graft survival in short-term and long-term follow-up [15-17]. There may be stages of antibody mediated change before development of acute or chronic AMR. We investigated whether any intervention can prevent acute and chronic AMR leading to inferior long-term graft survival. In our study, no subject or control developed acute AMR during the 3 year follow-up period. This study was focused more on long-term outcome of the renal allografts manifesting antibody mediated changes resulting from circulating DSA and/or C4d positivity in graft tissues. Majority of our subjects who manifested Cd4 positivity prior to the treatment became negative for C4d on a follow-up biopsy in a relatively short interval; median 17 days. Since this study did not include control patients who had positive C4d staining but did not undergo the treatment, it cannot be determined whether the treatment affected C4d positivity in the graft tissue or not. However, this finding suggests that C4d positivity in the tissue can be quite short-lived. It has been reported that approximately 3.3 % of recipients of a renal allograft who developed de novo DSA suffered graft failure by 6-month follow-up versus 1.3% of those who did not develop de novo DSA [13].

Interestingly, in our analysis of 11 DSA positive subjects who had undergone the series of treatments and been followed to 3 years, new versus old DSA or disappearance versus persistence of DSA did not affect long-term graft functional outcome. Our findings suggest that all DSA do not necessarily have negative impact on long-term graft outcome and persistent DSA is not necessarily related to inferior graft outcome compared to transient DSA. How the DSA mediated changes such as circulating DSA and C4d in the graft tissue can lead to chronic active antibody mediated rejection and graft failure is not well understood. It has been speculated that a spectrum of conditions from latent humoral response with only circulating antibody; silent humoral reaction with circulating antibody and C4d deposition; subclinical humoral rejection with circulating antibody and C4d deposition as well as tissue pathology; to humoral rejection with circulating antibody, C4d deposition, tissue pathology and graft dysfunction may exist [23]. However, it has also been reported that peritubular capillaritis can occur without C4d detected in the graft tissue [24, 25].

We suspected that PTC inflammation may predict progression to graft failure as previously reported [24]. In our study, no subject with PTC 1, 2, or 3 had improved graft function after the treatment (worse in 2/7 and no change in 5/7). This finding may suggest a negative impact of PTC inflammation on graft outcome, possibly through chronic AMR. However, a beneficial effect of the treatment on the long-term graft outcome cannot be assessed in the patients with PTC inflammation since there were no control patients with PTC inflammationin this study. It has been reported that tubulointerstitial and glomerular damage, once established, is irreversible, resulting in declining renal function and graft failure [26] and that interstitial fibrosis with inflammation at one year predicts transplant functional decline [27]. In the current study, IF/TA grade 0 and 1 tended to be associated with better functional outcome than IF/TA 2 and 3. We suspected a detrimental impact of coexisting ACR or the development of ACR during follow-up on the graft outcome as previously reported [28,29]. Our analysis suggested that coexisting ACR tended to be associated with poor functional outcome of the graft. A limitation of the current study is that multivariate analysis to assess the specific effect of individual variables could not be performed due to the relatively small sample size and heterogeneity of the subjects in their characteristics and clinical course as shown in Table 5, representing the usual patient population encountered in clinical settings.

In conclusion: on the basis of the analysis of the current study, we suggest that the series of treatments including 5 sessions of plasmapheresis, intravenous immunoglobulin and rituximab may play a beneficial role in management of recipients of a renal allograft manifesting circulating DSA and/or C4d in graft tissues to improve the long-term graft outcome when it is administered within the first year of transplant, especially in the presence of graft dysfunction.

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