Comparing Plasmapheresis plus IVIg with Plasmapheresis plus IVIg plus Rituximab on the Management of Suspicious Antibody-Mediated Acute Rejection in Kidney Transplant Recipients

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ABSTRACT

Background: There is no treatment of choice for the management of acute antibody-mediated rejection (ABMR) in kidney transplant recipients. Plasmapheresis ± intravenous immunoglobulin (IVIg) ± rituximab has been used in different regimens with contradictory results.

Objective: To compare three regimens of acute ABMR management including plasmapheresis + IVIg ± rituximab in two different rituximab regimens.

Methods: In this prospective, observational study kidney transplant recipients with suspicious ABMR were categorized into three groups. Group 1 patients were treated with plasmapheresis + IVIg. Groups 2 and 3 received weekly rituximab at a dosage of 375 mg/m^2 for either 4 doses (group 2 or high dose) or 2 doses (group 3 or low dose) in addition to plasmapheresis + IVIg.

Results: 8, 15, and 9 patients were categorized in groups 1, 2, and 3, respectively. There was no difference among the groups in terms of demographic and clinical characteristics of recipients and donors. Although, 1-year graft (37.5%, 60.0%, and 66.7% for groups 1, 2, and 3, respectively; p=0.308) and patients survival (75.0%, 86.7%, and 77.8% for groups 1, 2, and 3, respectively; p=0.730) were not significantly different among studied groups, graft survival was 22%–30% higher in rituximab-treated groups. Estimated glomerular filtration rate at 12th month of follow-up did not differ among groups (56.3±19.6, 57.3±20.6, 48.7±16.1 mL/min/1.73 m^2 for groups 1, 2, and 3, respectively; p=0.683). However, kidney function steadily improved over time in rituximab-treated patients.

Conclusion: Adding high or low doses of rituximab to plasmapheresis + IVIg comparably increased graft survival in suspicious acute ABMR kidney recipients and steadily improved kidney function among survived allografts over time.

KEYWORDS: Antibody-mediated acute rejection; Intravenous immunoglobulin; Kidney transplantation; Plasmapheresis; Rituximab

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INTRODUCTION

Acute antibody-mediated rejection (ABMR) is one of the major complications after kidney transplantation. Donor-specific antibodies (DSAs) against donor's human leukocyte antigens, ABO blood group and endothelial antigens are responsible for this complication [1]. Although the incidence of acute ABMR (5%–20%) is lower than that of acute cellular rejection (20%–50%), the prognosis is worse and the rate of graft loss within the first year is significantly higher in patients with acute ABMR (25%–40%) compared with those with acute cellular rejection (3%–7%) [2].

Diagnosis of acute ABMR is based on the Banff criteria using three components including histologic evidence of acute allograft injury, evidence of antibody interaction with vascular endothelium (*e.g.*, C4d deposits in the peritubular capillaries) in the biopsy specimen of the graft, and the presence of DSAs in the recipient's serum. Patients with the first two criteria but no evidence of circulating DSA are considered suspicious for acute ABMR [3].

To date, there is no treatment of choice or approved medication for the management of acute ABMR [4]. Treatments reported in case series and small studies have been applied based on ABMR mechanisms [4].

Plasmapheresis is the most effective method to remove alloantibodies including DSAs out of the blood [5] and improved graft survival in some previous studies [6, 7]. Because of the antibody rebound occurring after plasmapheresis, intravenous immunoglobulin (IVIg) is administered after plasmapheresis sessions [8]. Combination of plasmapheresis and IVIg has been reported to be effective in the management of acute ABMR [8-10]. Rituximab, an anti CD-20 agent which is used for the treatment of lymphoma, has recently been used for the management of acute ABMR [5, 11-14]. Various treatment protocols with different combinations of the above-mentioned modalities/drugs have been used in case series.

Rituximab-containing protocols that have been used for acute ABMR management can be categorized into two groups: Some used rituximab in its high standard doses of 3–5 weekly doses of 375 mg/m^2, as approved for the treatment of lymphoma [11, 14, 15]; other studies used low doses of rituximab, *i.e.*, 1–2 doses, for the management of acute ABMR [12, 16-18].

This study was conducted to compare three groups of Iranian kidney transplant recipients who experienced acute ABMR, and who were managed with plasmapheresis plus IVIg regimens alone or with either high or low doses of rituximab.

PATIENTS AND METHODS

Study Design

In this prospective, observational study, we compared three groups of kidney transplant recipients who managed for suspicious acute ABMR between May 2014 and July 2016 in kidney transplantation wards of Imam-Khomeini Hospital Complex and Milad Hospital, Tehran, Iran. Recipients of kidney transplants from deceased or living donors with clinical and biopsy suspicious of acute ABMR who had received similar immunosuppressive regimen containing thymoglobulin induction, tacrolimus, mycophenolate, and prednisolone were included. Tacrolimus doses were adjusted for the desired whole blood concentrations of 8–12 ng/mL. All patients received prophylaxis for *Pneumocystis jirovecii*, cytomegalovirus and candidiasis using co-trimoxazole, ganciclovir/valganciclovir, and clotrimazole troche/nystatin suspension, respectively for a defined duration based on the centers' protocols.

Diagnosis of ABMR

In one of the studied centers, diagnosis of acute ABMR was primarily based on the clinical evidence which included sudden impairment in the function of the allograft including anuria and increase in serum creatinine concentration after a few days of having functional kidney. Since the centers' induction immunosuppression starting before the transplantation

surgery, consisted of thymoglobulin which strongly prevents acute cellular rejection, a sudden deterioration in the graft's function within a short period after transplantation in the absence of surgical complications, could be suggestive of acute ABMR. The center protocol lacked a routine protocol biopsy. We therefore included only those patients with clinical suspicious of acute ABMR who did have or accepted to have biopsies and whose biopsies were in favor of the diagnosis. Time to ABMR in these patients was defined as the time from transplantation to occurrence of the first sign of rejection (either increasing serum creatinine concentration or decreasing urine output, which occurred earlier). In this center, ABMR treatments were started by responsible nephrologists according to clinical ABMR suggestions as mentioned above and continuation of the treatment depended on the tissue biopsy findings. In another studied center, protocol biopsies were done after transplantation according to that center policy. In that center, the patients who were diagnosed with acute ABMR according to the results of protocol biopsy even without clinical symptoms and treated for acute ABMR were included in this study. Time to ABMR in these patients was defined as the time from transplantation to the date of tissue biopsy showing ABMR findings. DSA levels were not available for included patients. All allograft biopsies from both centers were evaluated by an expert nephropathologist in Imam Khomeini Hospital Complex based on Banff criteria [3].

ABMR Management Protocols

Suspicious acute ABMR episodes were treated by responsible nephrologists. Patients were categorized into three groups based on their ABMR treatment regimens: Group 1 patients underwent plasmapheresis on a daily or every other day basis with 35–40 mL/kg volume exchange during each session. These exchange volumes were replaced mainly by 5% albumin (prepared by dilution of 20% albumin in normal saline) and one or two units of fresh-frozen plasma if required, based on the patients' international normalized ratio. The number of plasmapheresis sessions was based on the patient's response to the treatment according to decrease in serum creatinine concentration and increase in urine output.

Patients who received rituximab (375 mg/m^2) on a weekly basis for four doses in addition to plasmapheresis plus IVIg treatment were categorized as group 2 (high-dose rituximab). Rituximab was administered on the plasmapheresis day after the completion of IVIg infusion. Since a significant amount of rituximab is removed by plasmapheresis [19], the next session of plasmapheresis was done 48–72 h after administration of the rituximab. Patients in group 3 received two weekly doses of rituximab (low-dose rituximab) in addition to plasmapheresis and IVIg, as mentioned for group 2. Steroid pulses were administered for all patients in all three groups as part of their anti-rejection therapy.

Measured Outcomes

Serum creatinine concentrations and estimated glomerular filtration rates using Modification of Diet in Renal Disease (MDRD) equation were compared among groups at the time of hospital discharge and at 6th and 12th month of follow-up after ABMR treatment. Number of functioning kidneys at hospital discharge as well as 6- and 12-month graft and patients survival were also compared among the three studied groups. Functional kidney defined as not going back to the dialysis. All patients were monitored during the study period for any possible/probable side-effects associated with their ABMR treatments.

Ethics

The study protocol was approved by local Ethics Committee, Tehran University of Medical Sciences, Tehran, Iran. All patients were provided written informed consent form for using their clinical and laboratory data from their medical reports.

Statistical Analysis

Data were analyzed using SPSS® for Windows® ver 14 (SPSS Inc, Chicago, IL, USA). Results are shown as frequency and percentage for nominal variables and as mean±SD or median (range) for quantitative variables with and without normal distributions, respec-

Table 1: Demographic and clinical characteristics of kidney transplant recipients and donors' characteristics in the three study groups. Values are either number, mean±SD, or median (range).

Recipient	Group 1 (n=8)	Group 2 (n=15)	Group 3 (n=9)	p value
Sex (F/M)	5/3	4/11	5/4	0.094
Age (yrs)	48.6±17.3	43.2±11.0	52.7±8.3	0.19
Retransplant (yes/no)	2/6	7/8	1/8	0.173
HD duration (m)	19 (0–96)	27 (0–282)	15 (8–84)	0.465
Cause of ESRD*				
DM	2	2	2	
HTN	0	3	2	
PCKD	2	0	2	0.323
Others	1	4	2	
Unknown	3	6	1	
Donor				
Deceased/Living	7/1	15/0	8/1	0.387
Donor sex (F/M)‡	2/5	5/9	3/5	0.928
Donor age (yrs)	36.3±14.3	40.4±10.6	45.4±16.9	0.431
Donor SCr† (mg/dL)	1.2±0.4	1.2±0.4	1.2±0.2	0.923

*DM: Diabetes mellitus; ESRD: End-stage renal disease; HD: Hemodialysis; HTN: Hypertension; PCKD: Polycystic kidney disease; †SCr: Serum creatinine concentration; ‡One data in each group was missed.

tively. One-way ANOVA and Kruskal Wallis tests were used, respectively, for comparing quantitative variables with and without normal distributions among the three groups. Qualitative variables were compared using χ^2 or Fischer's exact test. Linear regression was used to adjust the effects of confounding variables. A p value <0.05 was considered statistically significant.

RESULTS

A total of 32 patients (18 males and 14 females) enrolled in the present study; of them, eight patients were in group 1, 15 in group 2, and nine in group 3. Twenty-two (69%) were transplanted for the first time. The most frequent causes of ESRD were diabetes (19%) and hypertension (16%). There was no significant difference among the three groups in terms of demographic characteristics of kidney transplant recipients, their leading causes of ESRD, hemodialysis duration before transplantation, re-transplantation, and donors' characteristics (sex, age and serum creatinine concentration) (Table 1).

Of 32 patients studied, seven (88%) in group 1, 10 (67%) in group 2, and one (11%) in group 3 underwent ABMR treatment, based on clinical suggestions of ABMR. For all of them, findings of biopsies were compatible with suspicious acute ABMR. The remaining patients were diagnosed with ABMR and treated based on the results of protocol biopsy. All included patients had suspicious acute ABMR based on Banff criteria by having both criteria of presence of histologic evidence of acute allograft injury (findings such as capillary endothelial swelling, fibrin thrombi in glomerular capillaries, glomerulitis with infiltration of polymorphonuclear cells in glomerular/peritubular capillaries, acute tubular necrosis, endothelitis and endarteritis in vessels) and C4d deposits in the peritubular capillaries in the biopsy specimen of the graft.

Time to ABMR, number of patients who needed hemodialysis during ABMR process, maximum serum creatinine concentrations, and minimum eGFR during ABMR episodes did not significantly differ among the three groups (Table 2). The number of plasmapheresis sessions was not significantly different

Table 2: Characteristics of ABMR episodes. Values are either number, mean±SD, or median (range).

Variable*	Group 1	Group 2	Group 3	p value
Time to ABMR (d)	4.0±4.0 4 (0–11)	4.2±3.6 4 (0–12)	2.4±2.8 1 (0–8)	0.505
Dialysis on ABMR (yes/no)	5/3	12/3	6/3	0.619
Minimum SCr before ABMR (mg/dL)	1.8±1.0	4.3±2.5	4.6±2.6	0.162
Maximum eGFR before ABMR (mL/min/1.73 m^2)	47.4±32.0 46.2 (18.1–78.9)	28.4±32.0 15.9 (6.8–123.1)	17.7±13.0 12.3 (6.3–44.4)	0.119
Maximum SCr on ABMR (mg/dL)	6.5±3.3	8.1±2.6	8.0±3.3	0.532
Minimum eGFR on ABMR (mL/min/1.73 m^2)	13.3±11.0 6.8 (5.0–34.1)	8.3±4.1 7.4 (4.9–18.6)	9.7±10.4 6.5 (4.0–37.2)	0.504
Treatment				
Number of PP sessions	8.1±3.4	11.5±3.3	9.8±2.9	0.07
Total IVIg (g/kg)	1.9±0.5	1.9±0.4	1.5±0.7	0.143
IVIg after each PP session (mg/kg)	307.1±164.0	173.3±133.0	122.2±44.0	0.018

*ABMR: Antibody-mediated acute rejection; eGFR: estimated glomerular filtration rate; IVIg; Intravenous immunoglobulin; PP: Plasmapheresis; SCr: Serum creatinine concentration.

among the three groups of the study. Although the total doses of IVIg administered was not significantly different among three study groups, the mean IVIg dosage administered after each plasmapheresis session was significantly higher in group 1 (p=0.018) (Table 2).

Although not significant, number of functioning grafts at the time of hospital discharge, and the 6- and 12-month graft survival were higher among rituximab-treated groups 2 and 3 (Table 3). Group 3 patients were from the center where ABMR episodes were mostly diagnosed based on protocol biopsy when there were no clinical symptoms suggestive of ABMR. Two patients in group 2 were discharged from the hospital with non-functioning grafts. These patients had been anuric and gone back to dialysis at discharge time. However, the graft started to work about one month after hospital discharge.

eGFR at hospital discharge was significantly higher in group 1 patients (Table 3). While eGFR among functioning kidneys remained almost constant for group 1 patients, eGFRs steadily increased over time in rituximab-treated groups 2 and 3 (Table 3). One-year patients survivals did not significantly differ among the three groups (Table 3).

After adjusting for possible confounding variables—IVIg dose after each plasmapheresis session, total IVIg dose, number of plasmapheresis sessions, and minimum eGFR at the time of ABMR—the eGFR at 12th month of transplantation did not significantly differ among the three groups (Tables 4).

Patients were followed for any adverse effects during 12 months of follow-up (Table 4). Infectious and non-infectious complications during the follow-up period was not significantly different among the three groups. Late-onset neutropenia (LON) and interstitial lung diseases were the major non-infectious complications related to rituximab. LON occurred in 3 of 15 patients in high-dose rituximab group and 4 of 9 in the low-dose group. Some of them were treated with G-CSF administration. Interstitial lung disease happened in one patient in high-dose rituximab group. Both of these complications presented as delayed-onset complications.

DISCUSSION

This study compared three regimens of acute ABMR management including plasmapheresis plus IVIg regimens alone or with either high or low doses of rituximab in kidney transplant

Table 3: ABMR treatment outcomes. Values are either number or mean±SD.

Outcome*	Group 1	Group 2	Group 3	p value
Number of functional kidney at hospital discharge	4/8	8/15	8/9	0.154
SCr at hospital discharge (mg/dL)	1.3±0.3	2.2±0.6	1.8±0.3	0.005
eGFR at hospital discharge (mL/min/1.73 m^2)	51.4±4.6	33.0±6.4	38.8±9.9	0.005
SCr at 6th month of transplant (mg/dL)	1.2±0.2	1.5±0.3	2.2±1.8	0.334
eGFR at 6th month of transplant (mL/min/1.73 m^2)	56.9±19.9	53.8±17.5	39.2±18.0	0.169
SCr at 12th month of transplant (mg/dL)	1.2±0.2	1.6±0.8	1.4±0.4	0.639
eGFR at 12th month of transplant (mL/min/1.73 m^2)	56.3±19.6	57.3±20.6	48.7±16.1	0.683
Graft survival at 6th month of transplant	3/8	10/15	8/9	0.083
Grafts' survival at 12th month of transplant	3/8	9/15	6/9	0.308
Patients survival at 6th month of transplant	6/8	14/15	9/9	0.296
Patients survival at 12th month of transplant	6/8	13/15	7/9	0.730
Complications During follow-up				
Infectious complications (number of infectious episodes during one-year follow-up to total number of patients)				
Endocarditis	0	1	0	0.408
UTI	2	2	3	
CAP	0	1	3	
CMV infection	1	1	2	
Infection in surgical area	2	0	1	
Bacteremia	0	1	0	
Mucormycosis	0	0	1	
Diabetic foot infection	0	1	0	
Multiple source infections	1	1	0	
Anal warts	0	0	1	
Non-infectious complications				
Late-onset neutropenia	0	3	4	0.584
Proteinuria	1	3	1	
Interstitial lung disease	0	1	0	
Causes of death during 12 months of follow-up	Infection: 1 Complicated biopsy: 1	Infection: 2	Infection: 1 Unknown: 1	

*CAP: Community-acquired pneumonia; CMV: Cytomegalovirus; eGFR: estimated glomerular filtration rate; SCr: Serum creatinine concentration; UTI: Urinary tract infection.

recipients. Although not significant, one-year graft survival was 22%–30% higher among rtituximab-treated patients that is clinically important. There was no significant difference in patients survivals among three regimens of ABMR treatment. Although eGFR of functioning kidneys did not significantly differ among the three groups after 12 months of transplantation, it steadily increased during the first year in rituximab-treated groups while remained almost constant in those who did not receive rituximab. Of interest, as seen in two patients in this study, the effect of rituximab on the function of transplanted kidney may be of delayed onset.

Table 4: eGFR at 12th month of transplantation adjusted for confounding variables

Independent Variable*	Slope	SE	p value
Constant	53.673	34.739	0.151
group	-2.585	5.830	0.666
Minimum eGFR on ABMR	-0.190	1.168	0.874
Total IVIG (g/kg)	-9.157	9.250	0.343
IVIG in each session (mg/kg)	0.085	0.053	0.135
PP sessions number	0.969	1.685	0.577

*ABMR: Antibody-mediated rejection; eGFR: Estimated glomerular filtration rate; IVIg: Intravenous immunoglobulin; PP: Plasmapheresis

Previous studies on acute ABMR management with and without rituximab are small retrospective studies and case series that have reached different findings. Some concluded that addition of rituximab to the traditional treatment of ABMR, which consists of removal of antibodies by plasmapheresis with or without IVIg, may have additional benefit on graft survival [11, 14, 15]. Different treatment regimens have been used in these studies. Faguer, *et. al*., reported a 10-month graft survival rate of 75% among eight kidney transplant recipients with acute ABMR who were treated with 3–5 weekly doses of 375 mg/m^2 rituximab in addition to plasmapheresis (IVIg was only administered in one patient) [11]. During a randomized clinical trial, Zarkhin, *et. al*., compared two groups of 10 transpant recipients with ABMR. One group managed for acute ABMR with steroids and/or thymoglobulin; the second group received four weekly doses of 375 mg/m^2 rituximab in addition to steroid/thymoglobulin [15]. No IVIg and plasmapheresis was used in their study. The groups showed the similar 12-month graft loss of two grafts [15]. In a case-control study including 26 patients, Kaposztas, *et. al*., reported that although the graft survival was significantly better in the rituximab group (receiving rituximab plus plasmapheresis and IVIg) compared to the control group, which were managed with plasmapheresis and IVIg without rituximab (90% *vs.* 60%, p=0.005), the level of renal function was just slightly better in rituximab group [14]. In our study, the 12-month graft survival in rituximab-treated groups was comparable to the survival rate reported by Faguer, *et. al.* [11], and less than that reported by Kaposztas, *et. al.* [14], with somewhat similar ABMR treatment protocols. Although our results were comparable to the findings of Kaposztas, *et. al*., in that level of kidney functions one year after transplantation were comparable between patients who were treated with and without rituximab [14], our results showed a long-term slow but continuous beneficial effect of rituximab on allograft function over time.

Among the studies used low doses of rituximab, which refers to a dose that is lower than the standard regimen approved for lymphoma, some researchers reported satisfactory outcomes [12, 13, 16, 20-25]. One or two doses of 375 mg/m^2 rituximab were administered in most of these studies [12, 13, 16, 22-25]. In a retrospective study on 27 kidney transplant recipients who managed for acute ABMR with a single dose of rituximab (in addition to plasmapheresis without IVIg), a two-year graft survival rate of 85% was reported [16]. Mulley, *et. al.* reported a 20-month graft survival rate of 100% by administering a single dose of 500 mg of rituximab to ABMR patients in addition to plasmapheresis and IVIg [12]. A graft survival rate of 100% was also reported by Gomes, *et. al*., using a single 375 mg/m^2 dose of rituximab along with plasmapheresis and IVIg by retrospective assessment of four patients [24]. Conversely, some other studies reported no satisfactory results by treatment of ABMR patients with low doses of rituximab [17, 18, 26-29]. In a pilot study on seven patients managed for ABMR with a single dose of 375 mg/m^2 rituximab added to IVIg, 24-month graft survival rate was only 57% [26]. Plasmapheresis, which is considered a main part of ABMR treatment, was not considered in the treatment regimen in that study [26]. Waiser, *et. al*., also reported a low

18-month graft survival rate of 11% in ABMR patients managed with a single dose of 500 mg rituximab plus IVIg and plasmapheresis [18]. The authors suggested that less aggressive immunosuppressive treatment regimens compared with that used in other studies (*e.g.*, using less IVIg doses) [12, 13], fewer plasmapheresis sessions [11, 12, 14], and not administering thymoglobulin [11, 14, 30] would be reasons for less response in their study, as well as strict definition of ABMR used in their study with inclusion of patients with both positive biopsy findings for ABMR and DSAs [18]. Sautenet, *et. al.*, designed a randomized clinical trial on ABMR-experienced kidney transplant recipients comparing addition of one or two doses of 375 mg/m^2 of rituximab to IVIg and plasmapheresis regimen *vs.* plasmapheresis and IVIg without rituximab [17]. One graft had been lost in each group in this trial during the 12 month follow-up. The researchers concluded that no additional benefit was achieved by addition of rituximab to plasmapheresis and IVIg [17]. The primary endpoint of Sautenet's study [17] was the graft function on the 12th day of receiving rituximab, which seems to be so early for rituximab to work [31]. In the majority of patients, it takes 1–6 weeks for rituximab to completely deplete B-cells in the peripheral blood [31]. Comparable to our findings, Belliere *et. al.*, in a pilot study with two groups of patients who received a high dose (22 patients) or a low dose (17 patients) rituximab for the management of acute ABMR reported similar outcomes in the two groups [32].

In our study, the graft survival in patients treated with low-dose rituximab in combination with plasmapheresis and IVIg was lesser than those reported by Mulley, *et. al.* [12], and Gomes, *et. al.* [24]. Our results were somewhat similar to those of Belliere, *et. al.*, where no significant difference between ABMR-treated patients with low and high doses of rituximab was observed in terms of patients and graft survival [32]. Belliere, *et. al.*, [32] reported comparable eGFRs for patients treated with low and high doses of rituximab. In our study, although not significant, eGFR was about 9 mL/min/1.73 m^2 higher in high-dose rituximab group compared with that in low-dose group, which may be of clinical importance.

The non-significant difference among different treatment regimens in the present study and other similar studies may be due to the small number of patients included. Enrolling small number of patients is however, inevitable because of low incidence of ABMR [2].

In the present study, serum creatinine concentration and eGFR at the time of hospital discharge were significantly different among the three groups. eGFR seemed to be higher in those who did not receive rituximab. These outcomes may have some bias. Patients in the present study were visited by different nephrologists with different approaches for hospital discharge. Some nephrologists preferred to discharge patients from hospital when they started to response to therapy by decreasing in serum creatinine concentration to prevent prolonged hospitalization and its complications. In this setting, serum creatinine was higher when the patient was discharged. Other nephrologists preferred to keep the patient in hospital until the best response to therapy was achieved. In this setting the patients were discharged with lower serum creatinine concentrations.

As mentioned in the results section, eGFR and serum creatinine at the end of follow-up duration was not significantly different among the three groups. But, when we compared the serum creatinine and eGFR at hospital discharge and at 12th month after transplantation in each group, it seems that rituximab-treated groups improved graft functions over time compared to no-rituximab-treated patients.

Seven of 24 rituximab-administered patients showed LON. It seems that the incidence of LON did not correlate with rituximab dose. LON happened in 20% of patients in high-dose and in 44% of patients in the low-dose rituximab group. As reported previously, the incidence of LON, time to LON onset, and LON duration in rituximab-treated kidney transplant recipients with acute ABMR resemble those reported in patients who received

rituximab for the management of lymphoma or rheumatologic diseases [33].

This study had some limitations including the small sample size and observational nature of the study. Small sample size is the major limitation that is inevitable due to low incidence of acute ABMR. This low incidence of ABMR could not be easily overcome by designing multicenter studies due to different immunosuppressive protocols among different kidney transplant centers, different policies in taking kidney biopsies and ABMR diagnosis as well as ABMR treatment.

In conclusion, adding high or low doses of rituximab to plasmapheresis and IVIg slightly increased the 12-month graft survival in acute ABMR-experienced kidney transplant recipients. Although the level of kidney function 12 months after transplantation did not differ significantly among the three ABMR regimens, kidney function improved steadily and comparably over time in patients with adding either low-dose or high-dose rituximab to plasmapheresis and IVIg compared with patients who were treated with plasmapheresis and IVIg alone. About 30% of rituximab-treated kidney transplant recipients with ABMR may develop rituximab-induced late-onset neutropenia. Interstitial lung disease, although rare, may occur as a result of rituximab administration.

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