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Significance of *De novo* Donor-Specific Anti-HLA Antibodies in Renal Transplantation: A Single Center Experience

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Abstract

T cell-mediated rejection (TCMR) became controllable, and the long-term renal graft survival came to be obtained by the recent progress and innovation of the immuno-suppressants. Whereas the prophylaxis and control of antibody-mediated rejection (ABMR) caused by donor-specific anti-HLA antibody (DSA) are still insufficient and affect the long-term renal graft survival. DSA was classified roughly as follows: preexisting DSA existed in the patients before renal transplantation (RTx), and *de novo* DSA produced in the patients after RTx. There are many reports about the effect that preexisting DSA gives to a renal graft, and the treatment for ABMR with preexisting DSA is established to some degree. In contrast to preexisting DSA, it cannot be said that *de novo* DSA are considered enough at present. In this study, we examined the impact that *de novo* DSA gave to a renal graft in 40 RTx patients under treatment in our hospital. Although there was no significant difference as to the renal graft function in DSA positive and negative group, the renal graft survival showed the tendency that was better in a DSA negative group than a positive group (85% vs. 55%, P=0.0553). We perform monitoring of the *de novo* DSA positively and should contribute to the prognosis improvement of the renal graft in future.

Keywords: Donor-specific anti-HLA antibody; Renal transplantation; Pre-existing DSA; *De novo* DSA; Antibody-mediated rejection

Introduction

By progress, the invention of the immuno-suppressants, long-term graft survival became to be obtained in renal transplantation (RTx) whereas, the control of the process leading to chronic rejection from antibody-mediated rejection by donor-specific anti-HLA antibodies (DSA) is insufficient so far. In other words, most currently available immuno-suppressants assumed the cellular immunity to be a target, and it is difficult to prevent chronic rejection due to the humoral immunity. Terasaki described that HLA antibodies were causes about all leading to chronic rejection from hyperacute rejection [1,2]. It is an urgent problem to elucidate the impact that DSA gives to a renal graft to obtain further long-term graft survival in RTx. In renal transplant patients who monitored postoperative DSA at Mito Medical Center, we examined the impact that donor-specific anti-HLA antibodies gave RTx graft retrospectively.

Materials and Methods

Patients

We conducted this retrospective observational study to examine forty patients who visited Mito Medical Center for treatment after RTx in present. Pre-transplant cross-match test of all patients was negative. Forty patients were thirty-one living donor and nine cadaveric RTx. Of the patients, twenty-nine were male and eleven were female, aged of 50.9 ± 10.5 (mean ± SD; range 30-80) years. In this study, we referred to the impact that post-RTx DSA gave for RTx prognosis (Table 1).

Methods

We collected data for patient age, gender, frequency and kind of RTx, history of blood transfusion and pregnancy, and graft survival. We evaluated laboratory data as follows: serum creatinine (S-Cr: mg/dL), calculated estimated glomerular filtration rate (eGFR: mL min^{-1} 1.73 m^{-2}), urine protein (UP: g/day) and post-RTx DSA (*de novo* DSA; class I and class II). We perform flow PRA as a DSA screening test. All patients do at least once of postoperative renal biopsy. The renal graft tissue obtained by renal biopsy received immuno-fluorescence and considered whether C4d was stained, all data were collected from medical records to perform this retrospective study. A total of forty RTx patients were enrolled in this study and divided to the DSA positive and negative groups. Each twenty patients were in the both groups. We examined correlation between DSA and the prognosis of the RTx (Table 2).

Statistical analysis

Results are given as means value. Paired t-test was used for comparison of the DSA positive and negative patients. All analyses were performed as two-tailed; P-values of < 0.05 were considered as statistically significant.

Results

The status of patients was listed in Table 1. S-Cr level was 1.57 ± 0.72 mg/dL, eGFR was 39.9 ± 16.0 mL min^{-1} 1.73 m^{-2}, and UP was 0.68 ± 0.71 g/day respectively. Sixteen patients were received pre- and post-transplant blood transfusion and six patients had pregnant experience. In twenty-eight patients, the graft survival was obtained. Table 2 was shown that there were patients in the DSA positive group who received blood transfusion and re-RTx as compared with the DSA negative

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group. In the DSA positive group, nine patients were only in Class I positive, eight patients were only in Class II positive and three patients were in both positive. No significant change in either renal graft function or graft survival was observed between these three groups.

Similarly, the laboratory test results of renal graft in both groups are shown in Table 2. S-Cr levels were 1.77 ± 0.92 mg/dL in the DSA positive group and 1.33 ± 0.48 mg/dL in the DSA negative group, showing no statistically significant difference. The comparison between the DSA positive and negative groups revealed no statistically significant difference in the eGFR and urine protein during the observation period (39.1 ± 16.1 vs. 42.4 ± 16.3 mL min^{-1} 1.73 m^{-2}, NS).

C4d deposition to renal tissue was found in twelve patients, and all cases were in the DSA positive group. C4d deposition was found in eight of twelve renal graft loss patients, and nine patients were in the DSA positive group. Though a graft survival rate tended to be high in the positive group, there was not the statistically significant difference in both groups (55% vs. 85%, P=0.0553).

Discussion

The rejection of the renal transplantation is divided into T cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR). The control of TCMR was almost enabled by the progress and innovation of immuno-suppressants, but ABMR measures are future clinical problems. ABMR are classified according to etiology

Items	Numbers
Number of patients	40
Gender	
Male	29
Female	11
Age (years)	50.9 ± 10.5 (range: 30-80)
Kind of RTx	
Living	32
Cadaver	8
Frequency of RTx	
1st	32
2nd	7
3rd	1
History of blood transfusion	16
History of pregnancy	6
Number of Graft survival	28
DSA positive	20
S-Cr (mg/dL) (N=32)	1.57 ± 0.72 (range: 0.77-3.68)
eGFR (mL min-1 1.73 m-2) (N=32)	39.9 ± 16.0 (range: 14.0-73.9)
urine protein (g/day) (N=23)	0.68 ± 0.71(range: 0.04-2.92)

Value are mean ± Standard Deviation (SD).
P-value by paired t-test.
P-value of < 0.05 were considered statistically significant.
RTx: Renal Transplantation.
DSA: Donor-Specific Anti-HLA antibody.
S-Cr: Serum Creatinine.
eGFR: Estimated Glomerular Filtration Rate.

Table 1: Background of patients.

Items	DSA positive	DSA negative	P-value
Number of patients	20	20	-
Gender			
Male	16	13	NS
Female	04	07	
Age (years)	52.9 ± 11.6	49.0 ± 9.0	
	(range: 30-80)	(range: 34-65)	
Kind of RTx			
Living	17	15	
Cadaver	3	5	
Frequency of RTx			
1st	13	19	
2nd	6	1	-
3rd	1	0	
History of blood transfusion	12	4	
History of pregnancy	3	3	
DSA positive			
Class I	9		
Class II	8		
Class I+II	3		
S-Cr (mg/dL)	1.77 ± 0.92	1.33 ± 0.48	NS
eGFR (mL min-1 1.73 m-2)	39.1 ± 16.1	42.4 ± 16.3	NS
urine protein (g/day)	0.67 ± 0.91	0.60 ± 0.57	NS
Number of C4d deposition	12	0	
Number of Graft survival	11 (11/20; 55%)	17 (17/20; 85%)	0.0553

Value are mean ± Standard Deviation (SD).
P-value by paired t-test.
P-value of < 0.05 were considered statistically significant.
RTx: Renal Transplantation.
DSA: Donor-Specific Anti-HLA antibody.
S-Cr: Serum Creatinine.
eGFR: Estimated Glomerular Filtration Rate.

Table 2: Comparison of post-RTx DSA positive and negative patients.

either preexisting DSA or *de novo* DSA. Preexisting DSA existed in the patients before RTx, and *de novo* DSA produced in the patients after RTx. According to Aubert et al. [3] report, compared with patients with ABMR caused by preexisting DSA, patients with ABMR caused by *de novo* DSA showed increased proteinuria and more transplant glomerulopathy lesions. Moreover, it was reported graft survival rate in *de novo* ABMR was inferior to preexisting DSA ABMR. The results of our study showed that there was much graft loss for *de novo* DSA positive group. The poor prognosis of the renal graft was suggested by presence of the DSA.

There are several reports as to the difference over DSA class I and II. In our study, renal graft function and a prognosis did not have significant difference in Class I and II.

Lefaucheur et al. [4] reported that the presence of the preexisting DSA was assumed as risk factor of graft loss regardless of class I and II.

On the other hand, Fidler et al. [5] reported that class II or both of class I and II positive were assumed as risk factor of graft loss. In our study, it was unrelated to class I, II and renal graft function and

graft survival. We considered this result occurred by study limitation. Limitation of our study was a retrospective observational study performed at a single center with a very small number of patients. Therefore, future examination is necessary.

C4d deposition to endothelial cells is considered to be an important index of the complement activation of ABMR [6,7]. Twelve patients had C4d deposition only in the DSA positive group, and eight patients of them fell into graft loss at our hospital.

It was suggested that presence of DSA and C4d affected the prognosis of the renal graft from this study. At present, although monitoring about the preexisting DSA is performed, we should monitor the *de novo* DSA in future.

In present, a transplant surgeon and a coordinator strongly suggest to perform transplant-renal biopsy for the recipients with proteinuria. However, a renal graft biopsy may be refused by a sense of fear of the patients, and it is a serious problem in thinking about early diagnosis, early treatment of the ABMR.

Limitation

Our study had a limitation. This study was a retrospective observational study performed at a single center with very small number of patients. And, in late years RTx of our country is approximately 1,500 cases a year. In addition, it is the present status in our area that there are extremely few RTx with approximately 5-10 cases a year. The patients in this study became the small group from these reasons.

Conclusion

Needless to say, the control of the DSA is important to the long-term survival of the renal graft. However, because all the relations of the DSA to ABMR were not elucidated, future further study is necessary.

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