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Posttransplant de novo donor specific HLA antibody monitoring and clinical outcomes: a single-center experience

Nurettin Ay[1], Vahhac Alp[1], Şeymus Kaya[2]

[1]Department of General Surgery, Organ Transplant Center, University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[2]Department of Pathology, University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

ABSTRACT

Objectives: Despite the improvements in early-term outcomes of kidney transplantation, late-term graft failure still remained as a critical problem. De novo donor specific antibodies (DSA) developing against direct human leukocyte antigens (HLA) are the significant risk factors for shortened graft survival in the previously non-sensitized cases. The purpose of this study is to evaluate the clinical outcomes of de novo DSA development in the kidney transplant cases.

Methods: The present study included 121 (alive/cadaver: 106/15) of 148 (alive/cadaver: 125/23) cases who were not previously sensitized (PRA and DSA negative) and undergone kidney transplantation between August 2012-January 2018. DSAs of the cases without expected declines in creatinine levels in the polyclinic follow-ups and postoperative early-term were evaluated. Renal biopsy was performed in the cases encountered with > 2000 mean fluorescence intensity (MFI) de novo DSA against HLA-A, HLA-B, HLA-DR. Treatment protocol of plasmapheresis+intravenous immunoglobulin (IVIG)+rituximab (in the cases without clinical response) was administered in the cases with antibody-mediated rejection (AMR) detected by renal biopsy. In addition, the presence of de novo non-DSA was also evaluated in the cases. The presence of de novo was encountered by identifying the specificities of anti-HLA antibody specificities using Luminex single antigen beads in the recipient serum.

Results: De novo DSA (antibodies against HLA-A, HLA-B, HLA-DR and HLA-DQ) were monitored in 23 cases. DQ positivity was detected in 10 cases. MFI values were > 4000 and 2000-4000 in 8 and 2 cases, respectively. De novo non-DSA was found in 19 cases. Biopsy was performed in 8 cases due to the development of MFI > 2000 de novo DSA against HLA-A, HLA-B and HLA-DR and the findings of acute humoral rejection (AHR) were encountered in 2 cases. Additionally, acute humoral rejection was diagnosed in 1 case that developed de novo non-DSA. Two cases were diagnosed with AHR by biopsy although no de novo DSA or non-DSA developed and renal graft loss occurred in these two cases.

Conclusions: The fact that routine DSA monitoring in all the cases provided no significant contribution to the outcomes of our study may contribute to the debates on the necessity of DSA monitoring in the patients with low immunological risk.

Keywords: De novo DSA, kidney, transplantation, monitoring

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***Address for correspondence:** Nurettin Ay, MD., University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Department of General Surgery, Organ Transplant Center, Diyarbakır, Turkey. E-mail: nurettinay77@hotmail.com, Tel: +90 412 2580074/2348*

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Despite the improvements in early-term outcomes of kidney transplantation, late-term graft failure still remained as a critical problem [1]. Current studies demonstrated that antibody-mediated humoral tissue injury is responsible for more 60% of the late graft losses [2-4]. De novo donor specific antibodies (DSA) developing against direct human leukocyte antigens (HLA) are the significant risk factors for shortened graft survival in the previously non-sensitized cases. The presence of DSA may be associated with antibody-mediated rejection (AMR) and cause shortened graft survival [5-7]. That fact orientated the researchers to investigate the HLA antibodies [8, 9]. The purpose of the present study is to evaluate the clinical outcomes of de novo DSA development in the cases who underwent kidney transplantation.

METHODS

The present study included 121 (living/deceased: 106/15) of 148 (living/deceased: 125/23) caseswhowere not previouslysensitized (PRA and DSA negative) and undergone kidney transplantation between August 2012-January 2018. Ethics committee approval dated 17.01.2017 No:91 of the study was obtained from the Ethics Committee of University of Health Sciences Gazi Yaşargil Training and Research Hospital. All transplantations were performed after achieving negative T-cell crossmatch by flow cytometry and complement dependent cytotoxicity (CDC) methods. The cases without expected decline in the creatinine levels in the postoperative early term and those who received routine DSA assessment once at every 3 months for the first year and then once yearly were included in the study. The cases in whom this protocol could not be implemented were excluded from the study. Renal biopsy was performed in the cases encountered with > 2000 mean fluorescence intensity (MFI) de novo DSA against HLA-A, HLA-B and HLA-DR. Renal biopsies were evaluated according to the present Banff criteria at the time of biopsy. Treatment protocol of plasmapheresis+intravenous immunoglobulin (IVIG)+rituximab (in the cases without clinical response) was administered in the cases with humoral rejection detected by renal biopsy. In addition, the presence of de novo non-DSA was also evaluated in the cases. The presence of de novo DSAwas encountered by identifying the specificities of anti-HLA antibody specificities using Luminex single antigen beads in the recipient serum. The demographic and clinical characteristics of the patients were presented in Table 1.

Immunosuppression and Prophylaxis

Basiliximab (20 mg/day; at the day of operation and postoperative 4th day) and antithymocyteglobulin (ATG; for high-risk patients; 3 mg/kg during operation and 1.5 mg/kg at the postoperative 1st and 2nd days) were administered as the induction therapy. Methylprednisolone 1000 mg was administered intraoperatively. This dose was gradually tapered in the following days and switched to 20 mg oral prednisolone at the postoperative 6th day. Oral prednisolone dosage was reduced gradually to reach 5 mg a day at the first year after transplantation. Calcineurin inhibitors (CNI; tacrolimus: 0.1-0.15 mg/kg/day and cyclosporine: 6-8 mg/kg/day) and mycophenolate mofetil (MMF; 2g/day, by splitting into two doses) or Mycophenolate sodium (MMF; 1440 mg/day, by splitting into two doses) were administered for maintenance of the immunosuppression. MMF dose of 600 mg/m² was administered as split into two doses in the children. Everolimus (replaced by MMF at the 5th day) was added to the treatment protocol to be used together with tacrolimus in the cases with 2 ≥ mismatches. Target level of everolimus with tacrolimus was attempted to maintain between 4-8 mg/dL. However, everolimus was used instead of CNI in the cases supposed to develop thrombotic microangiopathy (TMA) because of use of CNIs and target level was attempted to maintain between 8-10 mg/dL. Trimethoprim/sulfamethoxazole (400 mg/day) and valganciclovir (900 mg/day) were administered for the prophylaxis of *Pneumocystis Jirovecii* (until the postoperative 6th month) and cytomegalovirus (CMV) (until the postoperative 3rd month), respectively. Delayed graft function (DGF) was defined as the need for dialysis in the posttransplant period. Graft loss was defined as return of the recipient to dialysis due to graft failure. Acute rejection was diagnosed by renal biopsy. Acute cellular rejection (ACR) was treated with intravenous pulse methylprednisolone and/or ATG therapy depending on the severity of rejection. The cases who were diagnosed or comorbid with AMR received the treatment of plasmapheresis+intra-

Table 1. Descriptive data of the kidney transplant cases

Characteristics	Data
Gender M/F	
Recipient	69/52 (57%/43%)
Donor	41/65 (39%/61%)
Age (years)	
Recipient	34.1 (11-68)
Donor	41 (10ay-71)
Follow-up period (months)	32.5 (1-68)
Living donor /deceased donor	106/15 (87.6%/12.4%)
Operation of donor (O/L)	
Open nephrectomy	81 (67%)
Laparoscopic nephrectomy	40 (33%)
Relationship	
Spouse	35 (33%)
First degree	41 (39%)
Second degree	19 (18%)
Third degree	3 (3%)
Fourth degree	2 (2%)
Unrelated	6 (5%)
Number of DSA studied patients	121 (81.7%)
Median DSA positive time	21 (4-56)
Preemptive	38 (36%)
Induction	
None	15 (13%)
ATG	67 (55%)
Basiliximab	39 (32%)
Incompatibility numbers	15 (12.3%)
1	4 (3.3%)
2	17 (14%)
3	42 (34.7%)
4	15 (12.4%)
5	17 (14%)
6	11 (9%)
Rejection	
Acute celluler	4 (2.7%)
Acute humoral	4 (2.7%)
Celluler + Humoral	1 (0.6%)
Graft loss	6 (4%)
CAN	1
Humoral rejection	2
BKN	1
RAP	1
FSGS recurrence	1
Death	2 (1.6%)
DGF	3 (2.4%)
Discharge creatinine (mg/dl)	1.14 (0.55-2.4)
Last creatinine level (mg/dl)	1.1 (0.49-4.34)
Length of hospital stay (days)	10.1 (5-42)

CAN = Chronic allograft nephropathy, BKN = BK nephropathy, RAP = Renal artery pseudoaneurysm, FSGS = Focal segmental glomerulosclerosis, ATG = Anti-tymocyte globülin, DGF = Delayed graftfunction M = Male, F = Female

venous immunoglobulin (IVIG) every other day.

Statistical Analysis

Statistical analysis was performed using SPSS Software Version 16. The probability of the variables for normal distribution was tested by analytic statistical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given as median values for non-normally distributed variables. Since study data were non-normally distributed between the groups (DSA, Non-DSA and non-anti-HLA); creatinine values were compared using Mann-Whitney U test. A *p-value* less than 0.05 was accepted as statistically significant.

Table 2. De novo DSA and de novo Non-DSA data

	n (%)
De novo DSA (A, B, DR)	
DSA NEGATIVE	111 (91.7%)
1000 < CLASS 2 < 2000	2 (1.6%)
CLASS 1 >2000	5 (4.1%)
CLASS 2>2000	2 (1.6%)
CLASS 1 and 2 > 2000	1 (0.8%)
De novo DSA (DQ)	
De novo Non-DSA	3 (2.5%)
DQ CLASS 2 > 4000	2 (1.6%)
2000 < DQ CLASS 2 <4000	8 (6.6%)
1000 < DQ CLASS 2 < 2000	19 (15.7%)

DSA = Donor specific antibody

RESULTS

Mean follow-up duration ranged between 1 and 68 months in 121 cases included in the study. Median follow-up period was 32.5 months. HLA antibodies were encountered in 42 (34.7%; de novo DSA: 23, de novo Non-DSA: 19) cases. De novo DSA (DSA-A, DSA-B and DSA-DR) were detected in 10 cases. De novo DSA MFI value was > 2000 in 8 (6.6%) of those cases. We have determined DQ positivity in 13 (10.7%) cases. MFI values were > 4000, 2000-4000 and 1000-2000 in 8, 2 and 3 cases with DQ positivity, respectively (Table 2). In the postoperative term, de novo DSA and de novo non-DSA developed in 21th (a range of 4-56 months) and 24th (a range of 4-45 months) months, respectively. However, no statistically significant difference was present between the times of development of de novo DSA also in the postoperative term. In addition, no statistically significant correlation was detected between development of DSA and recipient age, recipient gender, DGF and number of donor-recipient matches. Except the cases with occurrence of graft loss, recent creatinine levels of the patients without anti-HLA antibodies (non anti-HLA), with de novo DSA and de novo non-DSA patients were 1.18 ± 0.51 (0.50-4.34), 1.30 ± 0.58 (0.89-2.75), and 1.01 ± 0.28 (0.49-1.6), respectively. No statistically significant difference was found between the creatinine levels of the patients with non anti-HLA compared with de novo DSA and de novo non-DSA ($p = 0.819$ and $p = 0.401$, respectively). No statistically significant difference was detected also between the creatinine levels of the patients with de novo DSA and de novo non-DSA ($p = 0.189$). The findings of AMRwas encountered in 2 of the 8 patients with de novo DSA by renal biopsy (Table 3) (Cases 3 and 6). These two cases became DSA negative after plasmapheresis+intravenous immunoglobulin (IVIG) therapy. However they were found DSA positive again during their follow-ups. In the follow-ups; 3 of 6 DSA positive cases became negative without implementation of any treatment. The rest 3 cases remained positive. Besides, one case with develoment of non-DSA was diagnosed with AMR. AMR developed in one patient without de novo DSA and one patient with de novo DSA DQ positivity (Table 3) (Cases A, B and C).

DISCUSSION

Although many studies have determined the association between development of de novo DSA after kidney transplantation and an immunological phenomenon such as AMR, there is no consensus on routine DSA monitoring in the posttransplantation period. Routine DSA monitoring is not performed in the postoperative follow-ups in many centers. In our study, we have evaluated posttransplant DSA outcomes of 121 non-sensitized cases (the cases that do not require implementation of desensitization protocol in the preoperative period) and the association between these outcomes and AMR. HLA-antibodies were encountered in 42 (34.7%) cases. De novo DSA was detected in 23 (17.4%; antibodies against HLA-A, HLA-B,

Table 3. De novo DSA/Non-DSA and acute humoral rejection relationship with cases

Cases	DSA type and MFI values	MM count	Induction	Biopsy result	De novo DSA/non-DSA process	Treatment
1	Class I 3213 Class II 7428	4	ATG	The patient did not give approval	56th month	Cr level is stable Outpatient clinic follow-up
2	Class I 11089	4	ATG	CAN	51th month	Outpatient clinic follow-up
3	Class II 20182	3	Basiliximab	AHR	24th month	PE + IVIG Outpatient clinic follow-up
4	Class II 3441	3	Basiliximab	CAN	12th month	Outpatient clinic follow-up
5	Class I 4336	4	ATG	No rejection	26th month	Outpatient clinic follow-up
6	Class I 6583	4	ATG	AHR	18th month	Outpatient clinic follow
7	Class I 2356	0	No induction	CAN	8th month	Outpatient clinic follow
8	Class I 9482	0	ATG	No rejection	4th month	Outpatient clinic follow
A	De novo DSA (-)	2	Basiliximab	AHR	De novo DSA (-)	PE + IVIG; Graft loss
B	Class II 9654	3	ATG	AHR	De novo DSA (+ DQ)	PE + IVIG Outpatient clinic follow-up
C	Class I 32227 Class II 37124	3	ATG	ACR (+) AHR (+)	De novo DSA (-) De novo non-DSA (+)	PE + IVIG Graft loss

AHR = Acute Humoral Rejection, DSA = Donor specific antibody, ATG = Anti-tymocyte globülin Cr = Creatinine, CAN = Chronic allograft nephropathy, ACR = Acute cellular rejection, PE = Plasma exchange, IVIG = Intravenous immunoglobulin, MFI = Mean Fluorescence Intensity

HLA-DR and HLA-DQ) cases. DQ positivity was determined in 13 (10.7%) of those cases. The findings of AMR was observed in 2 of 8 cases with de novo DSA development. In addition, a case with de novo non-DSA development was diagnosed with AMR. AMR was also diagnosed by biopsy in two cases despite absence of de novo DSA development and graft loss occurred in these cases. A significant association of de novo DSA development with graft loss and reduced graft survival has been found also in the literature. Li *et al*. [10] have determined that 1-, 3- and 5-year survival rates of the patients with de novo DSA development were 92%, 77% and 69%, respectively. Whereas, these rates were 100%, 100% and 96% in the cases without de novo DSA development, respectively. The same study has encountered that occurrence of de novo DSA was not correlated with development of AMR with in the posttransplant first

6 months whereas occurrence of de novo DSA was found significantly correlated with development of AMR after posttransplant 6th month [10]. Time interval between the occurrence of posttransplant de novo DSA and development of rejection still remained unclear. The previous studies have suggested that de novo DSA development has no negative effect on graft function [11, 12]. Terasaki *et al*. [12] have carried out a 1-year prospective follow-up study in 23 centers and found that the rates of graft failure in the cases with and without development of anti-HLA antibodies were 6.6% and 3.3%, respectively. In the same manner, Süsal *et al*. [13] have emphasized the importance of postoperative DSA monitoring in the patients with high immunological risk and impaired graft function. However, debates on DSA are still ongoing. Although, some studies have stated that DSA positivity in the absence of rejection has no impact on graft survival, there are also other studies which have noted that early and late developments of DSA have similar impact on graft injury [14, 15]. Prajuli *et al*. [14] has denoted in his study that DSA positivity in the absence of rejection has no impact on graft survival. In that study, post-biopsy follow-up period was shorter than 3 years. That period may be inadequate to draw reasonable conclusions. In our study, 2 cases with DSA development were diagnosed with biopsy-proven AMR. However, 2 cases without detection of DSA were also diagnosed with AMR by biopsy. Non DSA was present in one of those cases and graft loss occurred in both cases. Another case in our study was HLA-DQ DSA-positive and diagnosed with AMR by renal biopsy. Even though, there is no consensus on DSA positivity and graft survival with all aspects in the literature, our outcomes are not exactly consistent with general literature. That may be resulting from the fact that number of DSA positive patients is not high enough to present significant outcomes. Ginevri *et al*. [16] have identified de novo DSA and de novo non-DSA in respectively 19 (23%) and 24 (29%) patients in their 4.3-year follow-up study on 82 pediatric cases with kidney transplantation. Median DSA development duration was 24 months and DSAs were mostly against HLA-DQ antigens. Of the 82 cases; 8 and 4 were C4d+ AAR and C4d- AAR, respectively. The development of DSA and late AMR were correlated. Median time to development of AMR was 1 year [16]. In the present time, the association between HLA-DQ antibodies and AMR was investigated by many study groups and numerous articles have been reported on this issue [17-19]. Willicombo *et al*. [19] have detected de novo DSA in 92 (18.2%) of 505 cases in their study and 50 (54.3%) of those cases were found to have HLA-DQ DSA. That study has identified a significant association between the presence of HLA-DQ DSA andAMR [19]. DeVos *et al* [20] have obtained similar outcomes and detected rejection in 21 of the cases with HLA-DQ antibody. The rate of 3-year graft survival was found statistically significantly lower in those patients [20]. HLA-DQ antibody was identified in 13 cases in our study. Only one patient was diagnosed with biopsy-proven AMR. However, diagnosis of subclinical AMR could not be established in the cases with HLA-DQ positivity since we did not perform routine renal biopsy. In our study, we determined the MFI cut-off values as 1000, 2000 and 4000. In our study, the relationship between these MFI values and AMR was not significant. There is no consensus on the MFI cut-off values. This value varies from clinic to clinic. Morris *et al*. [21]. They stated in their study that cases with MFI < 2000 may not be an obstacle for transplantation. Also, in another study, a significant difference was observed between cases with MFI < 1500 and cases with > 1500 in terms of graft survive [22].

Postoperative routine DSA monitoring in the patients with low immunological risk is not performed because of high-cost. However, it is a recommended procedure in the patients with high immunological risk. We have aimed to present a contribution to the studies that evaluated the association between routine DSA monitoring performed in our country and AMR.

CONCLUSION

Although, retrospective design of our study is a limitation, nevertheless, the fact that routine DSA monitoring is a high-cost procedure and that routine DSA monitoring in all the cases in our study provided no contribution to the outcomes of our study may contribute to the debate on necessity of routine DSA monitoring in the patients with low immunological risk.

Authors' Contribution

Study Conception: NA; Study Design: NA, VA;

Supervision: NA, VA; Funding: NA, VA; Materials: NA, VA; Data Collection and/or Processing: NA, VA, ŞK; Statistical Analysis and/or Data Interpretation: NA, ŞK; Literature Review: NA; Manuscript Preparation: NA and Critical Review: NA, VA, ŞK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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