Original Article

Korean J Transplant 2019;33:47-54
https://doi.org/10.4285/jkstn.2019.33.3.47

KJT

Clinical significance of donor-specific anti-HLA-DR51/52/53 antibodies for antibody-mediated rejection in kidney transplant recipients

Borae Geum Park[1,2], Younhee Park[1], Dong Jin Joo[3], Kyu Ha Huh[3], Myoung Soo Kim[3], Soon Il Kim[3], Yu Seun Kim[3], Hyon-Suk Kim[1]

[1]Department of Laboratory Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea;
[2]Department of Laboratory Medicine, Korea University Guro Hospital, Seoul, Korea;
[3]Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Background: The presence of donor-specific antibodies (DSAs) to human leukocyte antigen (HLA) increases the risk of antibody-mediated rejection (ABMR) after kidney transplantation (KT). However, the clinical relevance of anti-HLA-DR51/52/53 antibodies remains unclear because of their weak antigen expression. This study evaluated the association between anti-HLA-DR51/52/53 DSAs and ABMR.

Methods: We retrospectively reviewed the single-antigen-bead panel reactive antibody (single PRA) results of 130 patients tested between August 1, 2009 and March 6, 2015, based on clinical necessity after allograft KT. Single PRA analysis was performed using Luminex assay kits (Lifecodes LSA class I and II). We reviewed the clinical course and biopsy results of patients with anti-HLA-DR51/52/53 DSAs.

Results: Post-KT DSAs were identified in 89 of the 130 patients (68.5%), with 26 of 32 class I DSAs and 63 of 66 class II DSAs being immunodominant DSAs. Thirteen patients had anti-HLA-DR51/52/53 DSAs. Three patients with anti-HLA-DR51/52/53 immunodominant DSAs alone were diagnosed with biopsy-proven ABMR. One patient who developed anti-HLA-DR DSA 13 days after KT showed a rapid increase in anti-HLA-DR51 DSA and had biopsy-proven ABMR.

Conclusions: Although the expression of the HLA-DR51/52/53 antigen was weak, anti-HLA-DR51/52/53 DSAs might be correlated with biopsy-proven ABMR. Therefore, anti-HLA-DR51/52/53 DSAs must be evaluated as a cause of ABMR after transplantation.

Keywords: Donor specific antibody; Antibody mediated rejection; Human leukocyte antigen

INTRODUCTION

The presence of donor-specific antibodies (DSAs) to human leukocyte antigen (HLA) increases the risk of antibody-mediated rejection (ABMR) after transplantation [1]. The frequency of DSA detection after kidney transplantation (KT) ranges from 4% to >50% [2]. Therefore, HLA typing analysis for the donor and the recipient is performed before KT. Further, DSAs are monitored periodically and evaluated if ABMR is suspected after KT.

Sensitive and thorough evaluation of de novo DSA after KT is important because serological evidence of DSAs to HLA or other antigens is a mandatory criterion for diagnosing ABMR in kidney allografts according to the Banff classification [3]. Luminex technology facilitates the detection of anti-HLA antibodies and the monitoring of DSAs. According to the United Network for Organ Sharing policies, HLA typing of all loci, including HLA-A, -B, -Bw4,

Received March 14, 2019
Revised August 12, 2019
Accepted August 13, 2019

Correspondence to: Hyon-Suk Kim
Department of Laboratory Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2443, Fax: +82-2-364-1583
E-mail: kimhs54@yuhs.ac

HIGHLIGHTS

- HLA-DR51, -DR52, and -DR53 antigens are linked to general DR antigens originating from *DRB1* genes.
- HLA-DR51/52/53 antigen expressions are significantly weaker than general DR antigens.
- Anti-HLA-DR51/52/53 donor-specific antibody (DSA) might be correlated with antibody-mediated rejection (ABMR).
- The unbound anti-HLA-DR51/52/53 might be more easily detectable than other DSAs after ABMR has begun.
- HLA-DR51/52/53 typing is recommended for donors and recipients in kidney transplant.

-Bw6, -C, -DRB1, -DRB3 (-DR52), -DRB4 (-DR53), -DRB5 (-DR51), -DQA1, -DQB1, and -DPB1 antigens, is required for deceased-donor transplantation. However, the Korean Network for Organ Sharing policy mandates only HLA-A, -B, and -DRB1 typing. Moreover, most studies have focused on DSAs to class I HLA-A and -B and class II HLA-DRB1 and -DQB1 rather than DSAs to HLA-C, -DR51, -DR52, -DR53, -DQA1, and -DPB1. This is because the antigenicity of latter group is weaker than that of the former group [4-6].

Although the mRNA levels of *HLA-C* genes are similar to those of *HLA-A* and *-B* genes, the expression of HLA-C molecules on the cell surface is much lower than that of HLA-A and -B molecules. Therefore, the DSA to HLA-C seems to be less relevant than the DSA to HLA-A and -B in clinical situations [4]. On the other hand, the contribution of DR51/52/53 gene products to the total HLA-DR cell surface expression is considered to be minor because the transcription of the gene of DR51/52/53 is at least 5-fold lower than that of the *DRB1* gene [5,6]. Therefore, the expression of DR51/52/53 gene products is significantly lower than that of *DRB1* allelic products. HLA-DR51, -DR52, and -DR53 antigens encoded by HLA-*DRB5*, -*DRB3*, and -*DRB4* genes are considered to be weaker than HLA-DR antigens such as HLA-DR1 to -DR18 encoded by HLA-*DRB1* genes. Although HLA-DR51, -DR52, and -DR53 antigens are significantly weaker than general DR antigens originating from the *DRB1* gene, HLA-DR51, -DR52, and -DR53 antigens are always linked to DR antigens (Table 1). Therefore, HLA-DR51, -DR52, and -DR53 antigens should be included in HLA-DR typing analysis. Further, for antibody analysis, anti-HLA-DR51, -DR52, and -DR53 (-DR51/52/53) antibodies could be considered as DSAs.

To date, the clinical significance of anti-HLA-DR51/52/53 antibodies has not been largely considered in Korea. The purpose of this study was to evaluate the association between anti-HLA DR51/52/53 DSAs and ABMR.

Table 1. Linked genes between HLA-DRB1 and -DRB3/4/5

Gene	Coding protein	Linked HLA DR antigen
DRB3	Beta chain of DR52	DR11, DR12, DR13, DR14, DR17(3), DR18(3)
DRB4	Beta chain of DR53	DR4, DR7, DR9
DRB5	Beta chain of DR51	DR15(2), DR16(2)
None	None	DR1, DR8, DR10

HLA, human leukocyte antigen.

METHODS

Study Design

We retrospectively reviewed the single-antigen-bead panel reactive antibody (single PRA) results of 130 patients tested between August 1, 2009, and March 6, 2015. All donors and patients underwent HLA-A, -B, and -DRB1 typing before transplantation. All patients underwent KT with negative T- and B-cell complement-dependent cytotoxic cross-match results. During the follow-up monitoring of recipients, single PRA was requested based on clinical necessity, such as increased serum creatinine level (>1.4 mg/dL) after allograft KT.

If there was a positive reaction to any anti-HLA-C or -DQ antibody on the single PRA results, additional donor HLA-C or -DQ typing was performed. If donor HLA-DQ typing was not available, the HLA type was predicted using the Korean linkage disequilibrium data of DRB1-DQB1. This study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2015-0180).

HLA Typing

HLA-A, -B, and -DRB1 typing is routinely performed in KT. The HLA type was determined using a polymerase chain reaction (PCR)-based molecular typing assay, except in 18 patients who underwent KT before February 1, 1998. Molecular HLA typing was tested with PCR-sequence specific primer (SSP) using Micro SSP Generic DNA Typing Tray (One Lambda, Canoga Park, CA, USA) or Luminex PCR-sequence specific oligonucleotide probe using Lifecodes HLA SSO Typing (Immucor Transplant Diagnostics, Stamford, CT, USA).

The HLA-DR51/52/53 antigens were assigned according to the HLA-DRB1 typing results of the donor and the recipient. HLA-DR11, -DR12, -DR13, -DR14, -DR17, and -DR18 antigens are linked to HLA-DR52; HLA-DR4, -DR7, and -DR9 are linked to HLA-DR53; HLA-DR15 and -DR16 are linked to HLA-DR51; and HLA-DR1, -DR8, and -DR10 are linked to none of HLA-DR51/52/53 (Table 1).

Single PRA

Single PRA analysis was performed using Luminex assay kits (Lifecodes LSA class I and II, Immucor Transplant Diagnostics). All positive reactions were determined according to the manufacturer's protocol. The antibody intensities were graded according to the mean fluorescence intensity (MFI), as follows: weak (<2,999), moderate (3,000-9,999), and strong (>10,000). All DSAs against HLA-A, -B, -C, -DRB1, -DQB1, -DR51, -DR52, and -DR53 were evaluated. We selected cases with anti-HLA-DR51/52/53 DSAs and reviewed the clinical course and biopsy results of each patient. All 70 biopsy results could be obtained at the time of single PRA analysis.

RESULTS

DSAs with the Highest MFI Level (Immunodominant DSAs)

Of the 130 patients with elevated serum creatinine levels after KT, no DSA was detected in 41 (31.5%) and post-KT

Table 2. Distribution of the DSA with highest MFI level (immunodominant DSA) detected in 130 patients with elevated serum creatinine levels after kidney transplantation

Immunodominant DSA	Number of patients (%)	MFI range	Median follow-up day (range)
Class I	26 (20.0)		
Anti-HLA-A	9 (6.9)	1,653-17,249	2,811 (1,682-7,579)
Anti-HLA-A DSA alone	8 (6.2)		
Anti-HLA-A with class II DSA	1 (0.7)		
Anti-HLA-B	14 (10.8)	1,328-4,790	3,003 (68-8,542)
Anti-HLA-B DSA alone	12 (9.2)		
Anti-HLA-B with class II DSA	2 (1.5)		
Anti-HLA-C	3 (2.3)	1,755-4,656	1,109 (970-6,256)
Class II	63 (48.5)		
Anti-HLA-DR	23 (17.7)	1,543-16,203	2,834 (13-7,943)
Anti-HLA-DR DSA without class I DSA	19 (14.6)		
Anti-HLA-DR DSA with class I DSA	4 (3.1)		
Anti-HLA-DRB1 DSA with anti-HLA-DR51/52/53 DSA	10 (7.7)		
Anti-HLA-DRB1 DSA alone with or without class I DSA	10 (7.7)		
Anti-HLA-DR51/52/53 DSA alone with or without class I DSA	3 (2.3)		
Anti-HLA-DQ	40 (30.8)	1,105-20,611	1,739 (33-7,252)
Anti-HLA-DQ DSA alone	30 (23.1)		
Anti-HLA-DQ DSA with anti-HLA-DR DSA	8 (6.2)		
Anti-HLA-DQ DSA with class I DSA	2 (1.5)		
No DSA	41 (31.5)		2,346 (66-9,019)

DSA, donor-specific antibody; MFI, mean fluorescence intensity; HLA, human leukocyte antigen.

DSAs was identified in 89 (68.5%), including 32 (39.5%) class I DSAs and 66 (74.1%) class II DSAs. The median follow-up was 2,654 days (range, 13–8,542 days) after transplantation in patients who developed DSAs. Only nine patients had both class I and class II DSAs. Of the 63 patients with immunodominant DSAs against class II HLA, 23 had anti-HLA-DR immunodominant DSA and 40 had anti-HLA-DQ immunodominant DSA. Among them, eight patients had both anti-HLA-DR and anti-HLA-DQ DSAs. All of them showed higher anti-HLA-DQ DSA MFI than

Table 3. Clinical data and biopsy results of 10 patients who developed both anti-HLA-DR 51/52/53 DSA and anti-HLA-DRB1 DSA

HLA-DR typing		DSA to HLA-DRB1 or class I (MFI)	DSA to HLA-DRB3/4/5 (MFI)	Day after transplantation	Kidney biopsy
Recipient	Donor				
DR11, DR13, DR52, DR52	DR4, DR11, DR53, DR52	DR4 (2,802)	DR53 (1,252)	325	Transplant glomerulopathy, C4d(−), g0, ptc0
DR10, DR15, DR51	DR13, DR15, DR52, DR51	DR13 (12,654), A24 (2,599)	DR52 (13,131)	1,361	ABMR, C4d(+, diffuse), g2, ptc1
DR4, -, DR53	DR4, DR13, DR53, DR52	DR13 (13,859)	DR52 (5,252)	990	ABMR, C4d(−), g3, ptc0
DR15, DR4, DR51, DR53	DR15, DR13, DR51, DR52	DR13 (15,190)	DR52 (14,878)	2,671	TCMR, type 1B, ABMR, C4d(−), g1, ptc0
DR4, DR14, DR53, DR52	DR4, DR15, DR53, DR51	DR15 (10,736), A24 (2,344)	DR51 (15,615)	257	TCMR, type 2B, ABMR, grade II, C4d(+, diffuse) g0, ptc2
DR4, DR13, DR53, DR52	DR15, DR13, DR51, DR52	DR15 (6,763)[a)]	DR51 (12,850)	13	ABMR, C4d(+, diffuse), g0, ptc1
DR13, -DR52	DR7, DR13, DR53, DR52	DR7 (10,616)	DR53 (11,322)	3,622	ABMR, grade II, C4d(−), g0, ptc3
DR8,-	DR8, DR13, DR52	DR13 (11,372)	DR52 (14,261)	3,409	ABMR, grade II, C4d(+, diffuse), g1, ptc2
DR10, DR11, DR52	DR9, DR10, DR53	DR9 (15,822)	DR53 (2,692)	2,996	ABMR, grade II, C4d(+, diffuse), g1, ptc0
DR1, DR4, DR53	DR1, DR13, DR52	DR13 (16,203)	DR52 (2,711)	3,417	ABMR, grade II, C4d(+, diffuse), g0, ptc2

HLA, human leukocyte antigen; DSA, donor-specific antibody; MFI, mean fluorescence intensity; ABMR, antibody-mediated rejection; TCMR, T-cell-mediated rejection; g, glomerulitis; ptc, peritubular capillaritis.
[a)]Anti-HLA-DR15 (1,461) preformed DSA was detected before transplantation.

Table 4. Clinical review data and biopsy results of three patients with anti-HLA-DR 51/52/53 highest DSA without anti-HLA-DRB1 DSA

HLA typing (recipient/donor)	Age (yr)/sex	Type of transplant	Year after transplantation	DR51/52/53 (recipient/donor)	DSA (MFI)	Cr	Kidney biopsy
A2, A24, B52, -, Cw1, -, DR15, -/A2, -, B44, -, Cw1, -, DR15, DR7	58/Male	Living-related donor KT	20.5	DR51, -/DR51, DR53	DR53 (18,752) without other HLA antibodies	3.99	ABMR, grade II C4d(+, diffuse, g1, ptc2
A2, A11, B62, -, DR4, DR14/A2, A30, B64, B62, DR4, DR15	52/Male	Living-related donor KT	9.1	DR52, DR53/DR51, DR53	DR51 (17,848) without other HLA antibodies	1.70	TCR and ABMR C4d(+, diffuse, g1, ptc3
A2, A11, B46, B71, Cw1, Cw8, DR8, DR9/A24, A11, B35, B71, Cw3, Cw8, DR9, DR15	62/Male	Living-related donor KT	8.7	DR53, -/DR51, DR53	DR51 (12,172), A24 (1,498)	2.25	ABMR, grade II C4d(+, diffuse, g1, ptc3

HLA, human leukocyte antigen; DSA, donor-specific antibody; MFI, mean fluorescence intensity; Cr, creatinine; KT, kidney transplantation; ABMR, antibody-mediated rejection; TCR, T-cell-mediated rejection; g, glomerulitis; ptc, peritubular capillaritis.

HLA-DR DSA MFI. Of the 23 patients with anti-HLA-DR immunodominant DSA, 10 had HLA-DRB1 DSA with anti-HLA-DR51/52/53 DSAs, 10 had HLA-DR DSA alone, and three had HLA-DR51/52/53 immunodominant DSAs without HLA-DR DSA (Table 2). Three patients who had anti-HLA-DR class I DSA were also positive for anti-HLA-DR51/52/53 DSAs (Tables 3 and 4).

Clinical Review of Patients with Anti-HLA-DR51/52/53 DSAs

Ten patients had anti-HLA-DR51/52/53 DSAs plus anti-HLA-DRB1 DSA. Their clinical data are described in Table 3. One patient who had low MFI of DSAs to HLA-DR4 (MFI, 2,802) and DR53 (MFI, 1,252) was not diagnosed with ABMR. The remaining nine patients were diagnosed with acute or chronic ABMR according to the biopsy results. Two of them also had T-cell-mediated rejection (TCMR). One patient who developed anti-HLA-DR DSA at 13 days after KT had anti-HLA-DR15 (MFI, 6,763) with anti-HLA-DR51 (MFI, 12,850) DSAs. In this patient, anti-HLA-DR15 (MFI, 1,461) preformed DSAs were present before KT and increased rapidly just after transplantation.

Table 4 summarizes the clinical data of the three patients with anti-HLA-DR51/52/53 immunodominant DSAs without anti-HLA-DRB1 DSA. These three patients underwent living-related-donor KT 8.7–20.5 years earlier and were diagnosed with acute ABMR based on kidney biopsies. Anti-HLA-DR51 and -DR53 antibodies without the other HLA antibodies were detected in two patients. In the other patient, anti-HLA-DR51 antibody was detected with low MFI of anti-HLA-A24 DSA (MFI, 1,498).

Patients with Anti-HLA-DQ and Other DSAs

Forty patients had anti-HLA-DQ immunodominant DSAs, and 30 of them had anti-HLA-DQ DSA alone (Table 2). The clinical data of 10 patients with both anti-HLA-DQ and other DSAs are summarized in Table 5. Only 23 biopsy results were obtained for patients with anti-HLA-DQ DSAs, and four of them showed negative C4d staining results (Fig. 1). All of these four patients had only anti-HLA-DQ DSAs, and three of them showed low MFI (<2,999) of DSAs. Only one patient with anti-HLA-DQ DSA (MFI, 11,326) showed TCMR on biopsy.

DISCUSSION

DSAs to HLA-DR51/52/53 and HLA-DR antigens can be observed simultaneously because HLA-DR51/52/53 antigens are always linked to HLA-DR. In this study, both anti-HLA-DRB1 and anti-HLA-DR51/52/53 DSAs were detected in 10 of 20 patients with anti-HLA-DRB1 DSA. According to our results, the existence of anti-HLA-DR51/52/53 DSAs without the other HLA antibodies correlated with acute ABMR (Table 4). Although HLA-DR51/52/53 antigen expression is at least 5-fold lower than that of HLA-DRB1, our findings suggest that anti-HLA-DR51/52/53 DSAs can be clinically significant. Acco-

Table 5. Clinical data and biopsy results of 10 patients who developed both anti-DQ DSA and anti-HLA-DR or class I DSA

DSA to HLA-DQ (MFI)	DSA to HLA-DR or class I (MFI)	Cr	Day after transplantation	Kidney biopsy
DQ6 (7,583)	DR14 (4,843)	NA	3,670	ABMR, grade II, C4d(+, diffuse), g2, ptc1
DQ9 (9,432)	DR9 (8,633)	2.07	4,120	ABMR, grade II, C4d(+, diffuse), g0, ptc2
DQ2 (20,687)	DR7 (2,109)	2.56	4,681	Chronic ABMR, C4d(+, diffuse), g3, ptc1
DQ7 (12,702)	DR12 (453)	1.47	869	ABMR, grade II, C4d(+, diffuse), g1, ptc1
DQ8 (12,386)	DR4 (1,764)	3.18	3,095	Chronic ABMR, C4d(+, focal), g3, ptc1
DQ9 (17,644)	DR9 (15,822)	2.10	2,996	ABMR, grade II, C4d(+, diffuse), g1, ptc3
DQ7 (15,059)	DR11 (1,397)	2.34	1,785	Chronic ABMR, C4d(+, diffuse), g3, ptc2
DQ9 (15,609)	DR9 (658)	1.59	441	C4d(+/–, weak), g0, ptc3
DQ6 (9,456)	A2 (1,100)	2.02	265	ABMR, grade II, C4d(+, diffuse), g0, ptc2
DQ8 (8,035)	B44 (416)	NA	2,611	ABMR, grade II, C4d(+, diffuse), g2, ptc2

DSA, donor-specific antibody; HLA, human leukocyte antigen; MFI, mean fluorescence intensity; Cr, creatinine; NA, not applicable; ABMR, antibody-mediated rejection; g, glomerulitis; ptc, peritubular capillaritis.

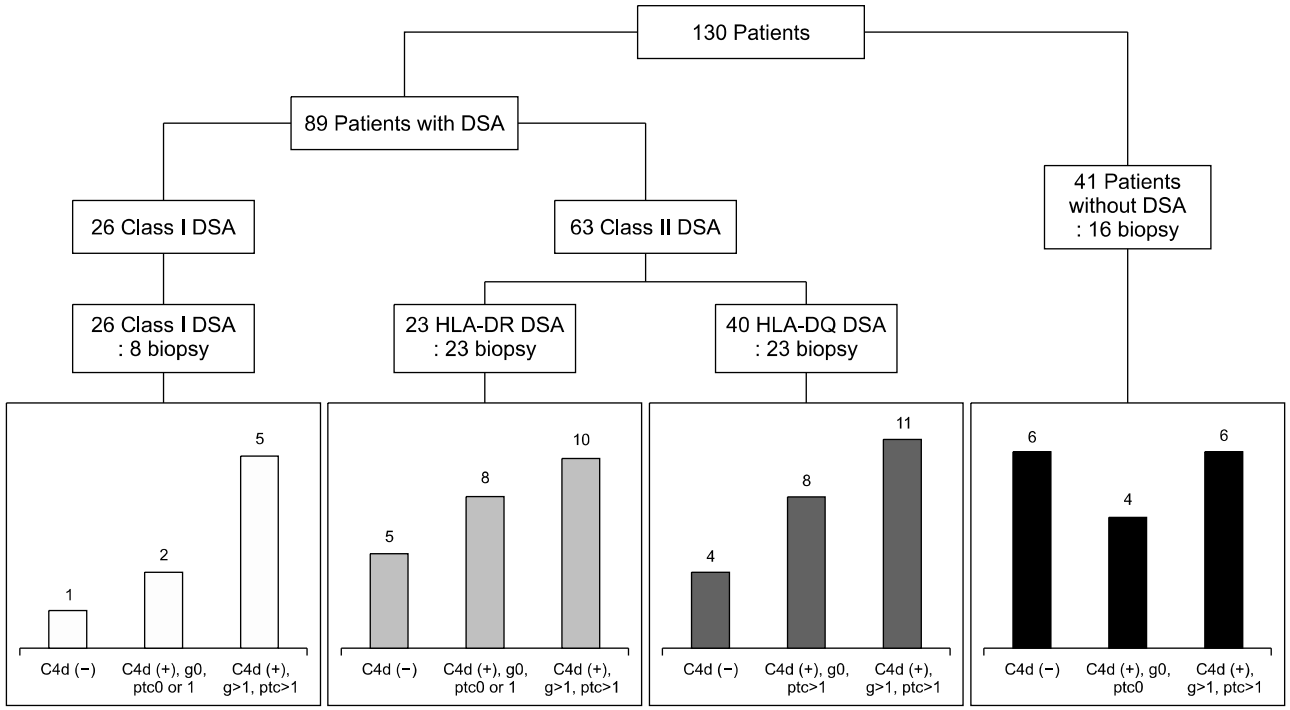

Fig. 1. Pathologic results according to immunodominant donor-specific antibody (DSA). A total of 70 biopsy results could be obtained at the time of DSA detection. HLA, human leukocyte antigen; g, glomerulitis; ptc, peritubular capillaritis.

rding to a previous report, not only HLA-A, -B, and -DRB1 mismatches but also HLA-DR51/52/53 mismatches have an independent impact on HLA allosensitization [7]. The risk of allosensitization was similar between HLA-A, -B, -DRB1, and -DR51/52/53 mismatches with odds ratios of 3.2, 3.4, 3.5, and 3.9, respectively [7].

Once a DSA forms, it binds to the kidney allograft. Therefore, DSA-negative ABMR is possible when all DSAs are bound to the allograft and cannot be detected in peripheral blood [8]. However, HLA-DR51/52/53 antigens are generally weaker than HLA-DRB1 antigens; therefore, the amount of target antigen to which the DSA can be bound is also small. DSA specific for HLA-DR51/52/53 is refractory to elimination before and after allograft nephrectomy [9]. These findings indicate that unbound anti-HLA-DR51/52/53 could be detected more easily than other DSAs after ABMR has begun.

In one patient who was diagnosed with acute ABMR only 13 days after transplantation, anti-HLA-DR51 DSA increased more rapidly than anti-HLA-DR15 DSA. Three other patients showed anti-HLA-DR51 or -DR53 DSA without anti-HLA-DR DSA and were diagnosed with biopsy-proven ABMR. These findings also indicated that unbound anti-HLA-DR51/52/53 could be detected more easily than anti-HLA-DR DSA.

However, there are several limitations in confirming anti-HLA-DR51/52/53 DSAs as a cause of ABMR. In patients with DSAs after KT, anti-HLA-DQ DSAs were the most frequently detected antigens and their MFI was higher than that of other DSAs in the study. HLA-DQ DSAs are a well-known cause of ABMR after KT. Therefore, HLA-DQ typing should be emphasized in the evaluation of KT. However, the focus of our study was anti-HLA-DR51/52/53 DSAs, and the small number of cases with anti-HLA-DR51/52/53 DSAs was the major limitation of this study. Further, we could not evaluate whether or not the DSAs formed de novo, because there were no single PRA results for the pre-KT status. Most important, the absorption of DSAs by the grafts is a well-known phenomenon after KT [10]. Therefore, it could be possible that the unbound anti-HLA-DR51/52/53 DSAs were detectable instead of the main cause of ABMR.

We did not perform HLA typing tests for HLA-DR51/52/53 but assigned the type according to the association

between HLA-DR51/52/53 and -DR. However, rare cases, with the exception of the associations between HLA-DR51 and -DR16 and between HLA-*DR53* and -*DRB1*07:01* genes, have been reported in the Korean population [11,12]. Therefore, molecular analysis for HLA-DR51/52/53 is necessary for these rare exceptions with genetic frequencies of 0.005 to identify the correct HLA-DR51/52/53 type. Moreover, allele-specific false-positive or -negative reaction is possible owing to the limited kinds of HLA-DR51/52/53 allele-specific beads in Luminex single PRA. However, HLA-gene of HLA-DR51/52/53 genes are less polymorphic, and homogeneity in haplotypic associations has been observed between HLA-*DRB1* and HLA-*DRB5* alleles in the Korean population [13]. Therefore, an allele-specific false reaction would be a rare finding.

In the single PRA assay, the antigen densities of HLA-DR51/52/53 on beads are relatively higher than those of other HLA antigens comparing with actual human condition. Therefore, there is a risk of overestimating the levels of antibodies to these antigens, and the results should be interpreted carefully [14]. Moreover, the MFI is not necessarily as high as the value indicates. The same limitations can be applied in assessing anti-HLA-C DSAs. Recently, the clinical relevance of anti-HLA-C DSA was reevaluated, and the results suggested that it likely leads to the development of acute ABMR [15]. Therefore, DSAs to weak HLA antigens, such as anti-HLA-DR51/52/53, should be considered as a cause of ABMR.

Despite the limitations, our study showed that anti-HLA-DR51/52/53 DSAs might be correlated with biopsy-proven ABMR. Therefore, anti-HLA-DR51/52/53 DSAs should be considered during the DSA evaluation after KT. On the basis of the results of our study, HLA-DR51/52/53 typing is recommended for all donors and recipients in KT.

ACKNOWLEDGMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding/Support

This study was supported by a faculty research grant.

Previous Presentation

This article is previously presented in the annual meeting of American Society for Histocompatibility and Immunogenetics (ASHI; September 28, 2015; Savannah, GA, USA).

ORCID

Borae Geum Park https://orcid.org/0000-0001-9710-9253
Younhee Park https://orcid.org/0000-0001-8458-1495
Dong Jin Joo https://orcid.org/0000-0001-8405-1531
Kyu Ha Huh https://orcid.org/0000-0003-1364-6989
Myoung Soo Kim https://orcid.org/0000-0002-8975-8381
Soon Il Kim https://orcid.org/0000-0002-0783-7538
Yu Seun Kim https://orcid.org/0000-0002-5105-1567
Hyon-Suk Kim https://orcid.org/0000-0001-5662-7740

Author Contributions

Conceptualization: BGP. Data curation: DJJ, KHH, MSK, SIK, YSK. Formal analysis: BGP. Funding acquisition: BGP, YP, HSK. Methodology: BGP, YP, HSK. Project administration: DJJ, KHH, MSK, SIK, YSK. Visualization: BGP. Writing - original draft: BGP. Writing - review & editing: BGP, YP, HSK.

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