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Detection of Antibodies Against Human Leukocyte Antigen Class II in the Sera of Patients Receiving Intravenous Immunoglobulin

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Background. IVIG is occasionally used for preventing and treating severe infections of patients who are to undergo transplantation. Administration of IVIG, which includes high-titer antibodies (Abs) against HLA class I and II, might have a substantial influence on the HLA Ab test results of these patients. However, this issue has remained unreported. **Methods.** Anti-HLA Ab titers were determined in 4 types of IVIG preparations, fresh frozen plasma, and the sera of 11 patients with hematological diseases before and after IVIG administration. **Results.** Although anti-HLA Abs were not detected in any of the fresh frozen plasma products, various anti-HLA class I and II Abs were detected in all 4 IVIG preparations. Six out of 11 patients who had received IVIG showed a low titer of anti-HLA class II Abs, which were not detected before IVIG administration. Conversely, no anti-HLA class I Abs were detected in any of the 11 patients. Furthermore, all 4 (100%) patients who were positive for anti-HLA class II Abs initially and were assessable became negative for anti-HLA Abs after the discontinuation of IVIG treatment (median, d 79; range, d 22–192). **Conclusions.** IVIG preparations consist of high-titer anti-HLA class I and II Abs, but the latter can be transiently detected in the sera of patients who had received IVIG. When these patients are screened for the presence of donor-specific Abs, some may be incorrectly deemed positive for HLA class II Abs. Thus, caution is necessary when only donor-specific Abs specific to class II HLAs are detected in patients.

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INTRODUCTION

The presence of donor-specific antibodies (DSAs) against unshared HLAs in recipients is a major obstacle for HLA-mismatched hematopoietic stem cell transplantation (HSCT)[1-3] and for HLA-mismatched solid organ transplantation (SOT).[4-6] When transplantation candidates are positive for DSAs, healthcare professionals should ensure that donors should not carry HLAs that are recognized by these DSAs because DSAs are associated with graft failure after allogeneic HSCT and SOT. IVIG is occasionally used for patients with hematological diseases such as immune thrombocytopenia and common variable immunodeficiency and for treating severe infections in patients with hematologic diseases that develop during chemotherapy, particularly in patients undergoing treatment to induce remission and who are to undergo HSCT.[7-11] IVIG preparations contain high-titer antibodies (Abs) against HLAs[12,13] because they are produced from the plasma of healthy donors, including multiparae. The recent use of IVIG for HSCT and SOT candidates may lead to false-positive DSA results. To test this hypothesis, we measured anti-HLA Ab titers in the IVIG preparations and the sera of patients who received IVIG.

MATERIALS AND METHODS

This study (#2017-069) was approved by the institutional review board of Kanazawa University, Japan, and was

conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Anti-HLA Abs were tested using LABScreen PRA and Single Antigen Beads (regular beads; One Lambda/Thermo Fisher, Canoga Park, CA) for class I (HLA-A/-B/-Cw) and class II (HLA-DR/-DP/-DQ),[14,15] and measured with a Luminex100 flow analyzer (Luminex, Austin, TX). The number of alleles examined was: 39 HLA-A, 82 HLA-B, 30 HLA-Cw, 50 HLA-DR, 30 HLA-DQ, and 39 HLA-DP. EDTA was added to a final concentration of 0.005 M to avoid the prozone phenomenon. The normalized mean fluorescence intensity (MFI) was defined as (MFI of sample beads – MFI of negative control beads) to remove the background signal. MFI of >1000 was defined to be positive (please see lot numbers in Table S1, SDC, http://links.lww.com/TXD/A324). Four types of IVIG preparations, fresh frozen plasma (FFP; n = 3), and the sera of 11 patients who received IVIG (5 g [n = 3], 10 g [n = 1], 15 g [n = 4], 20 g [n = 1], 80 g [n = 1], and 90 g [n = 1]) were used in this study. The 4 types of IVIG preparations were as follows: (1) freeze-dried sulfonated human normal immunoglobulin (Kenketsu Venilon-I, The Chemo-Sero-Therapeutic Research Institute, Japan; n = 3, lot # SVA354, SVA362, SVA368); (2) polyethylene glycol–treated human normal immunoglobulin (Venoglobulin IH 5%, Japan Blood Products Organization, Japan; n = 3, lot # A638VX, X620VX, X619VXA); (3) freeze-dried ion-exchange-resin–treated human normal immunoglobulin (GAMMAGARD, Shire, USA; n = 3, lot # LE08R008AB, LE08R022AB, LE08S002AB); (4) pH4-treated acidic normal human immunoglobulin (subcutaneous injection) (Hizentra, Immune Globulin Subcutaneous [Human], 20% Liquid, CSL Behring, USA; n=3, lot # 4382500004, P100000190, P100001319). IVIG were serially diluted (from 1:1, ending 1:64) with PBS (PBS; pH 7.2) and were added to the wells containing the antigen-coated microbeads.

RESULTS

Anti-HLA Abs in Fresh Frozen Plasma and IVIG

Although the 3 fresh frozen plasma products did not exhibit any reactivity with HLA class I and II alleles, all 4 IVIG preparations showed broad reactivity across HLA class I (A, B, and Cw) and II (DR, DQ, and DP) alleles, with an impression of more consistent and higher reactivity for HLA class I Cw alleles when they were diluted 1:1 (undiluted), 1:2, and 1:4 with PBS (Figure 1; Figure S1, SDC, http://links.lww.com/TXD/A324).

Patient Demographics

Patients who received IVIG were selected from those undergoing treatment at Department of Hematology of Kanazawa University Hospital from March 20XY to July 20XY+1. Patients' characteristics are shown in Table 1. Briefly, the patients had a variety of hematological diseases and were treated with IVIG dose range of 5–90 g, and 8 of 11 patients received allogeneic HSCT. The total dose of IVIG (g) was estimated within 28 days (between d X–28 and d X) before the initial anti-HLA Abs test post-IVIG (d X) because anti-HLA Abs were not detected on day 22 post-IVIG administration (90 g) during the follow-up test (patient no. 11; Table 1), and the half-life of IgG is between 7 and 21 days. Anti-HLA Abs tests were performed once before the administration of IVIG (median, d –42; range, d –96 to 0) and likewise, once after the final dose (median, d 1; range, d 0–8). In the case of a positive anti-HLA Ab test, 1 follow-up test was performed for each patient at some point after the termination of IVIG treatment (median, d 79; range, d 22–192; Table 1).

Anti-HLA Abs in the Sera of Patients Treated With IVIG

Six of 11 (55%) patients who received IVIG (5–90 g) showed low-titer anti-HLA class II Abs (MFI = 1004–3040) post-IVIG that were not detected before IVIG administration (Table 1; Figures 2 and 3). Conversely, no anti-HLA class I Abs were detected in any of the 11 patients. The anti-HLA class II Ab detection rate was 1 out of 4 (25%) in patients who received 5 or 10 g of IVIG and 5 out of 7 (71%) in patients who received ≥15 g of IVIG (Table 1). Of note, a patient with primary ITP (patient no. 11) who received high-dose IVIG showed an increased titer of anti-HLA Ab with sequential doses of IVIG (Figure 3). This patient exhibited a relatively low level of anti-HLA class II Abs (MFI ≤1710) on March 15, 20XY, before administration of IVIG. This may be related to her pregnancy history. The 5 other cases (patient no. 4, 6, 7, 8, and 10) who turned from negative to positive for anti-HLA class II Abs also reflected the anti-HLA Abs in infused IVIG (Figure 2). These anti-HLA class II Abs in the patient with ITP (patient no. 11) became undetectable on day 22 after IVIG administration. In total, all 4 (100%) patients (patient no. 4, 6, 8, and 11) who were positive for anti-HLA class II Abs initially and were available for follow-up became negative for anti-HLA Abs after the discontinuation of IVIG treatment (Table 1); thus, anti-HLA class II Abs in the sera of patients were derived from IVIG preparations.

Clinical Course of Patients Who Underwent HSCT After Administration of IVIG

Five of the 8 cases of allo-HSCT had anti-HLA class II Abs, in which only 1 patient (case no. 4) had DSA before engraftment. One case who had low to moderate levels anti-HLA class II Abs, which were not donor specific (median MFI, 1557; range 1016–3040), before engraftment, experienced graft failure (patient case no. 7; Figure 2C). After the graft failure, we found that the donor of patient no. 7 had HLA-DQA1*03:02/03:02, DQB1*03:03/03:03, DPA1*01:03/02:02, and DPB1*02:01/05:01 alleles, but anti-HLA DPB1*02:02/DPA1*01:03 Ab (MFI 2712) in the serum before engraftment was not DSA despite the fact that its serotype was HLA-DP2. Interestingly, no graft failure was observed in the patient (case no. 4) who underwent allo-SCT in the presence of donor-specific anti-HLA class II Ab after IVIG administration (MFI 1098 in DRB1*16;02 in patient case no. 4; Figure 2A); this may be related to the low level of DSA detected. The patient with DSA underwent no desensitization treatments and complement-binding activity tests before allo-SCT because the level of DSA was low (MFI = 1098).

DISCUSSION

IVIG is produced from the plasma of healthy donors, and it contains high IgG levels. Abs to viruses (eg, HBsAb, HBcAb, HTLV-1/2 Ab, rabies Ab), bacteria and autoimmune Abs present in IVIG products have resulted in false reactive serological results,[16-26] thus, reactive Ab results shortly

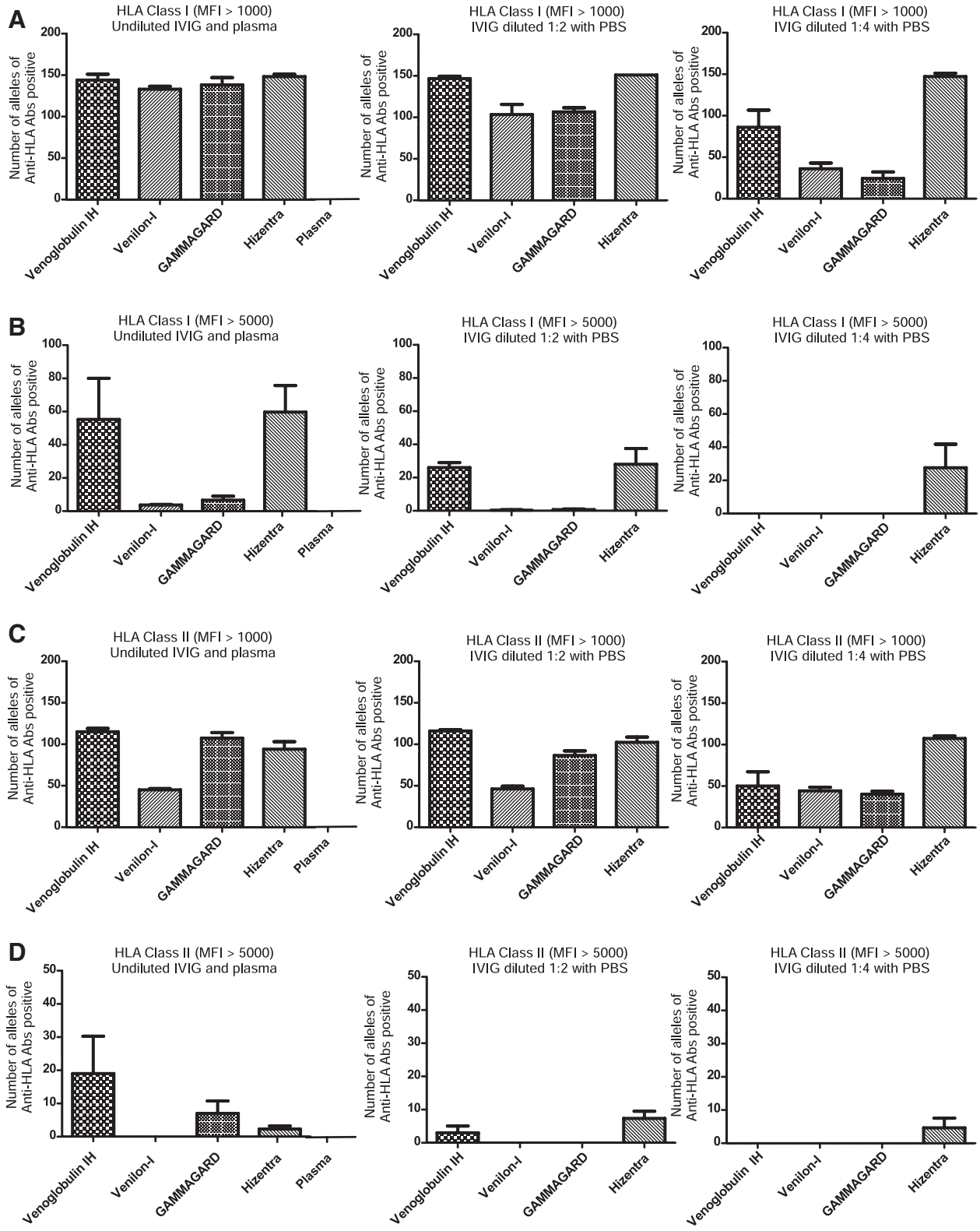

FIGURE 1. The number of alleles of anti-HLA [class I (A, B, and Cw) and II (DR, DQ, and DP)] Abs identified in each IVIG preparations (n = 3) and plasma (n = 3) derived from healthy donors. The allele number of (A) anti-HLA class I Abs (MFI >1000) and (B) anti-HLA class I Abs (MFI >5000), (C) anti-HLA class II Abs (MFI >1000), and (D) anti-HLA class II Abs (MFI >5000). Abs against 151 HLA class I and 119 HLA class II alleles were analyzed. All IVIG preparations were diluted 1:1 (undiluted), 1:2, and 1:4 with PBS, and the plasma was undiluted. Abs, antibodies; MFI, mean fluorescence intensity.

after IVIG may represent passive Ab infusion rather than endogenous Ab production in response to infection or vaccination. Positive results of anti-HLA Abs shortly after IVIG administration should be interpreted cautiously because they might show passive transfer instead of true infection or immunity derived from vaccination. There are several previous

TABLE 1.

Patients' characteristics, time courses of IVIG administration, and results of anti-HLA antibodies tests

Patient's number	Age at the first IVIG infusion	Sex	Disease and treatments	Date of anti-HLA Abs test pre-IVIG (d IVIG treatment) and its result	Date of allo-SCT	IVIG	Date of IVIG treatment	Total dose of IVIG (g)[a]	Date of anti-HLA Abs test post-IVIG (d post-IVIG) and its result	Date of follow-up anti-HLA Abs test post-IVIG (d post-IVIG) and its result	Results of engraftment post-allo-SCT
1	33	M	AML post-allo-SCT	Negative on May 24, 20XY (d −79)	August 4, 20XY	Venoglobulin IH 5%	5 g/d on August 11, 20XY	5	Negative on August 11, 20XY (immediate post-IVIG)	NA	Yes
2	46	F	AA post-allo-SCT	Negative on May 18, 20XY+1 (d 0)	January 25, 20XY+1	Venoglobulin IH 5%	5 g/d on May 18, 20XY+1	5	Negative on May 19, 20XY+1 (d 1)	NA	Yes
3	58	F	MM post-auto-SCT	Negative on April 2, 20XY+1 (d 0)	NA	Venoglobulin IH 5%	5 g/d on April 2, 20XY+1	5	Negative on April 3, 20XY+1 (d 1)	NA	NA
4	44	M	AML post-allo-SCT	Negative on April 21, 20XY (d −96)	July 19, 20XY	GAMMAGARD	5 g/d on July 26 and August 2, 20XY	10	Positive (DSA, max MFI 1781) on August 9, 20XY (d 7)	Negative on October 2, 20XY+1 (d 192)[b]	Yes
5	78	F	ML post-chemo Tx	Negative on July 16, 20XY+1 (d 0)	NA	Venoglobulin IH 5%	5 g/d on July 16, 17, and 18, 20XY+1	15	Negative on July 20, 20XY+1 (d 2)	NA	NA
6	20	F	ML post-allo-SCT	Negative on May 23, 20XY+1 (d −30)	June 15, 20XY+1	Venoglobulin IH 5%	5 g/d on June 22, 29 and July 5, 20XY+1	15	Positive (non-DSA, max MFI 1877) on July 6, 20XY+1 (d 1)	Negative on January 9, 20XY+2 (d 35)[c]	Yes
7	44	M	AML post-allo-SCT	Negative on July 12, 20XY (d −13)	July 13, 20XY	GAMMAGARD	5 g/d on July 25, 26, and 27, 20XY	15	Positive (non-DSA, max MFI 3040) on August 4, 20XY (d 8)	Died due to TRM post-allo-SCT	No
8	45	F	ALL post-allo-SCT	Negative on May 22, 20XY (d −53)	July 26, 20XY	Venoglobulin IH 5%	5 g/d on July 14, 17, and August 2, 20XY	15	Positive (non-DSA, max MFI 1018) on August 9, 20XY (d 7)	Negative on May 28, 20XY+1 (d 123)[d]	Yes
9	61	M	MDS post-allo-SCT	Negative on June 12, 20XY+1 (d 0)	June 5, 20XY+1	Venoglobulin IH 5%	5 g/d on June 12, 19, 26, and July 3, 20XY+1	20	Negative on July 4, 20XY+1 (d 1)	NA	Yes
10	55	F	ALL post-allo-SCT	Negative on July 4, 20XY+1 (d 0)	February 21, 20XY+1	Venoglobulin IH 5%	5 g/d on July 4 and 15 g/d on July 18, 19, 20, 21, 22, 20XY+1	80	Positive (non-DSA, max MFI 1727) on July 23, 20XY+1 (d 1)	Receiving IVIG due to parvovirus B19 infection as of April 20XY+2	Yes
11	26	F	Primary ITP	Positive (max MFI 1710) on March 15, 20XY (d 0)	NA	Venoglobulin IH 5%	10 g/d on March 15 and 20 g/d on March 16–19, 20XY	90	Positive (max MFI 2977) on March 20, 20XY (d 1)	Negative on April 10, 20XY (d 22)	NA

[a]Total dose of IVIG (g) within 28 d before the first anti-HLA Abs test post-IVIG.
[b]Last IVIG was administered on March 24, 20XY+1 (5 g/d).
[c]Last IVIG was administered on December 5, 20XY+1 (5 g/d).
[d]Last IVIG was administered on January 25, 20XY+1 (5 g/d).

AA, aplastic anemia; Abs, antibodies; ALL, acute lymphocytic leukemia; allo-SCT, allogeneic stem cell transplantation; AML, acute myelocytic leukemia; auto-SCT, autologous stem cell transplantation; DSA, donor-specific antibody; F, female; ITP, immune thrombocytopenia; M, male; MDS, myelodysplastic syndrome; MFI, mean fluorescence intensity; ML, malignant lymphoma; MM, multiple myeloma; NA, not applicable; TRM, treatment-related mortality; Tx, therapy.

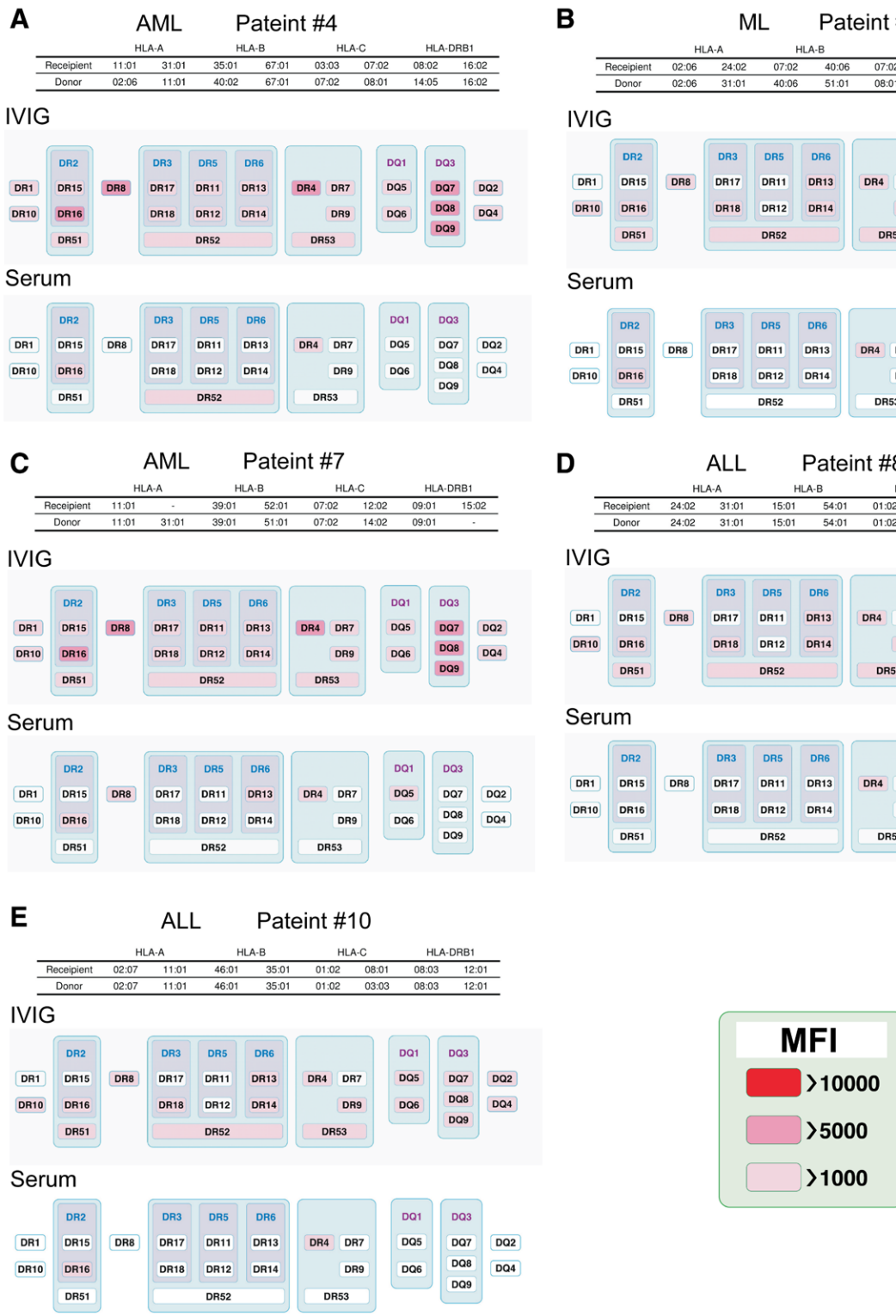

FIGURE 2. Types of anti-HLA Abs that were detected in administered IVIG (upper) and in the sera of patients (lower) who received allogeneic stem cell transplantation. (A–E) Patient no. 4, 6, 7, 8, and 10, respectively. Pink color HLA denotes the titer of anti-HLA Abs with MFI >1000. IVIG was not diluted. Anti-HLA Abs against 151 class I and 119 class II alleles were assessed. Abs, antibodies; ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; MFI, mean fluorescence intensity; ML, malignant lymphoma.

reports of anti-HLA Abs in the preparations of IVIG.[12,13,27-29] Ravindranath et al showed that therapeutic preparations of IVIG have high levels of HLA (Ia and Ib) Abs[12] and HLA class II Abs.[13] In our study, all 4 IVIG preparations showed reactivity with various HLA class I and II alleles, and the high reactivity with Cw is similar to that reported in a previous report.[12] According to our results, only the anti-HLA class II Abs were detected in the sera of patients, excluding the anti-HLA class I Abs. Meanwhile, the individual anti-HLA class I Abs, class II Abs, and both of these Abs were detected in 96

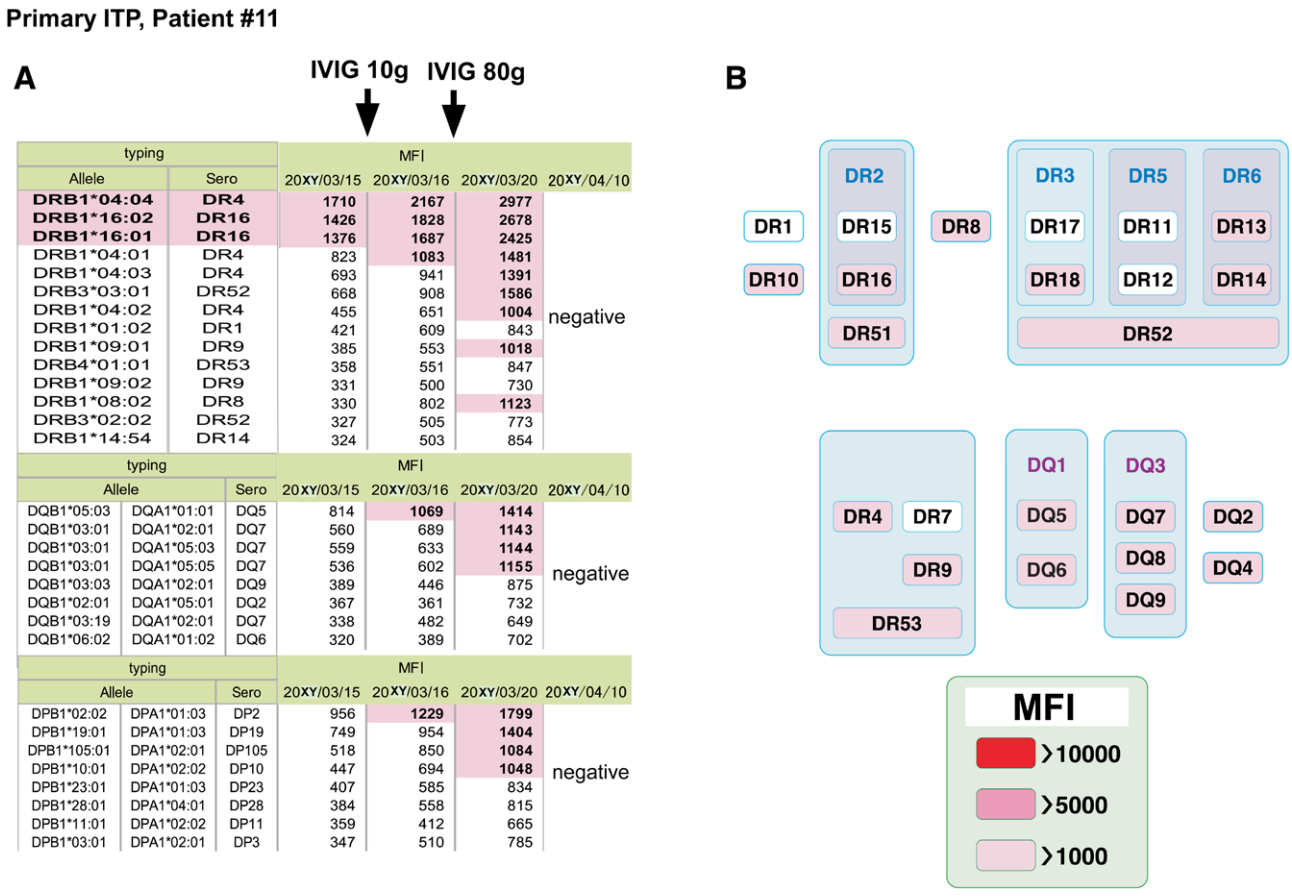

FIGURE 3. Time course of anti-HLA class II antibody titer (A) in a patient with primary ITP (patient no. 11) who received 90 g of IVIG that contained anti-HLA class II Abs (MFI was between 1000 and 5000. IVIG was not diluted) (B). ITP, immune thrombocytopenia; MFI, mean fluorescence intensity.

(52.2%), 38 (20.7%), and 50 (27.2%) of 184 cases, respectively, according to our experience regarding mostly hematologic diseases (unpublished data, 2019). The reason for the detection of only anti-HLA class II Abs in this study remains unclear. Unlike HLA class I antigens that are expressed on many cells, HLA class II antigens are only expressed on antigen-presenting cells, and therefore, the class II Abs may not have been sufficiently absorbed. Ravindranath et al[12] reported that inhibition experiments with synthetic peptides showed that HLA-E shares epitopes with HLA-Ia alleles. Anti-HLA class I Abs in IVIG may have been absorbed by HLA class E, which is expressed on many cells. Morales-Buenrostro et al[30] reported that although HLA Abs are normally not found in subjects who have not been immunized by pregnancies, transfusions, or transplants, normal male individuals have HLA Abs; 12% of the male subjects had high levels of anti-HLA class I Abs (MFI >5000) and not anti-HLA class II Abs. These anti-HLA class I Abs are likely to be produced in crossreactive epitopes found in microorganisms, ingested proteins, and allergens, making them natural Abs. The natural anti-HLA class I Abs in the IVIG preparations might be absorbed with allergens or ingested proteins in the patients' bodies after their administration. In short, only anti-HLA class I Abs and not class II Abs may have been absorbed by HLA class E, which is expressed on many cells and binds anti-HLA class I Abs, or by allergens or indigested proteins which may bind anti-HLA class I Abs in IVIG. By contrast, Stoclin et al[29] reported a case of transfusion-associated acute lung injury in a patient who was treated with IVIG (80 g/2 d). Donor-specific anti-HLA B8, DR11, and DQ7 Abs were detected in the patient serum, most likely derived from IVIG. Anti-HLA class I Abs may have been detected in this case related to the high dose of IVIG used. This finding indicates that anti-HLA class I Abs could be detected in sera when higher doses of IVIG are administered.

One of the serious issues derived from anti-HLA Abs is the incidence of graft failure in HLA-mismatched hematopoietic stem cell and organ transplantations. In the HSCT, 1 out of 8 cases of allo-SCT experienced graft failure (patient no. 7; Figure 2C). To investigate the reason of graft failure, we further assessed the HLA-DQ and DP alleles of the donor of patient no. 7 because we had not assessed these alleles in our clinical practice. However, the anti-HLA class II Abs of the patient did not crossreact with any HLA-DQ and DP of the donor, showing that the anti-HLA class II Abs were not DSAs. In addition, 1 patient (patient no. 4) who underwent allo-SCT had low-level anti-HLA class II DSA (MFC 1098 in DRB1*16;02) after IVIG administration, but graft failure did not occur (Figure 2A). In short, 1 patient with graft failure had anti-HLA Abs, but they were not donor specific, and 1 patient with donor-specific HLA Ab preengraftment related to IVIG did not experience graft failure. The relationship between IVIG-derived anti-HLA Abs, graft failure, and solid organ rejection needs to be examined using

a larger data set. Several mechanisms of action have been attributed to IVIG,[31] including inhibition of the complement activation cascade, expansion of regulatory T cells, inhibition of the proinflammatory effects of monocytes, neutralization of chemokines or cytokines, reductions in surface expression of class II HLA molecules secondary to dendritic cell modulation, and inhibition of apoptosis. Overall, IVIG has profound immunomodulatory effects and is not toxic to hematopoietic cells.

The presence of DSAs in sera of recipients remains a major obstacle to HLA-mismatched transplantation; this includes cases of HLA-haploidentical transplants and HLA-mismatched cord blood SCT and SOT. Desensitization treatments, including IVIG, plasma exchange, rituximab, and bortezomib,[32-36] have been performed before transplantations in an effort to reduce the level of DSAs. IVIG in sensitized patients may confound the assessment of DSAs post-IVIG and further studies are needed in this area.

There are some limitations to our study. First, we evaluated only small number of patients (n = 11) as an exploratory study; likewise, anti-HLA Abs levels were routinely assessed only once before, during, and after IVIG administration. Therefore, multicenter studies that include a large number of patients will need to be considered to generalize the findings, particularly those related to the detection of anti-HLA class II Abs after administration of IVIG. Second, the kinetics of anti-HLA Abs in sera of patients who were treated with IVIG were not evaluated in detail because varying amounts of IVIG were administered, and the single time points featured in our Ab assessments were not uniformly distributed with respect to the period of IVIG administration.

In conclusion, high-titer Abs against HLA class I and II were detected in IVIG, but the latter could be transiently detected in the sera of patients who received IVIG. When these patients are screened for the presence of DSAs, some may be incorrectly deemed positive for HLA class II Abs. Therefore, DSAs after IVIG administration must be interpreted with caution.

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