

Immunogenicity of red cell alloantigens in the Japanese population

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ABSTRACT

Aims: To elucidate transfusion-related blood group antigen immunogenicity among Japanese, a retrospective single center study was done.

Methods: For 49,884 transfusion recipients from late 2006 to early 2018, antibodies were tested with two techniques: saline immediate spin test and polyethylene glycol-enhanced indirect antiglobulin test. From male recipients with an average of 4.2 donor exposures, we calculated the immunogenicity of blood group alloantigens with a mathematical model.

Results: Indirect antiglobulin test detected 638 alloantibodies, 391 (1.53%) among 25,563 women and 247 (1.02%) among 24,321 men. Anti-E (489.1 per 100,000), followed by anti-Le^a (238.6 per 100,000) and anti-Fy^b (100.2 per 100,000) were most frequently found in the whole. Immunogenicity calculations among male recipients based on 4-donor exposure revealed Jt^a (67.4 per 1000, 95% CI: 1.7–323.3) as the possibly highest potency antigen, followed by: Le^a (23.5 per 1000, 95%

CI: 17.4–29.6), Di^b (20.1 per 1000, 95% CI: 0.5–109.3), E (11.9 per 1000, 95% CI: 9.4–14.4), and Jk^a (5.7 per 1000, 95% CI: 1.7–9.6) among Japanese male recipients.

Conclusion: Jr^a and Diego blood group antigens might be highly immunogenic in the Japanese population, but more recipients would need to be investigated to establish statistical significance.

Keywords: Alloantibody, Alloimmunization, Blood group alloantigen, Immunogenicity

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INTRODUCTION

Exposure to alloantigens by blood transfusion, pregnancy/delivery, or transplantation may provoke host immune responses leading to alloantibody formation [1]. Red cell alloantibodies formed as a result of such exposures are implicated in maternofetal incompatibility, which can lead to hemolytic disease of the fetus and newborn, and acute or delayed hemolytic transfusion reactions [2].

Although guidelines pertaining to the clinical significance of various alloantibodies are widely available, guidance about how to maximize detection of significant antibodies, while minimizing detection of insignificant antibodies, is lacking. Even so, there has been a downward trend in the incidence of delayed hemolytic transfusion reactions over the past several decades, possibly because of improved antibody detection systems [2, 3].

Further, using data to maximize detection of warm reactive antibodies and minimize detection of naturally occurring antibodies reactive only at room temperature, we were able to calculate blood group antigen immunogenicity within the Japanese population with the “Giblett equation” [4] and similar algorithms for platelet antigen exposure during pregnancy [5], modified by Tormey and Stack [6–8] corrected for antibody persistence rates and multiple red blood cell (RBC) exposures. At present, blood group antigen immunogenicity data is generally derived from Caucasian-dominant populations; to our knowledge this is the first comprehensive report of immunogenicity in an Asian cohort.

MATERIALS AND METHODS

Patients

Between September 2006 and February 2018, a total of 49,884 patients (25,563 women (51.2%) and 24,321 men (48.8%)) were included, with no age exclusions. Patients with any congenital diseases, including hemophilia, hemoglobinopathy, autoimmune disorders, hematological diseases, any immunodeficiency, those receiving immunosuppressive medicine and/or immunoglobulin, plus recipients of solid organ transplants and/or hematopoietic stem cells, were likewise not excluded from this study. Antigens other than ABO and D were not matched for transfusion recipients in whom alloantibodies were not detected. This study protocol was approved by the Ethics Committee of Fukushima Medical University (#29152, August 8th, 2017).

Methods for antibody testing and identification

Alloantibody screening and identification were conducted with standard tube techniques [1, 9]. Four-cell panels comprised of Surgiscreen (three cells) and Di^a positive cells (both from Ortho Clinical Diagnostics, NJ, USA) were used for antibody screening. In the saline-immediate-spin (Sal-IS) method, two drops of patient serum or plasma were mixed with one drop of each panel cell, centrifuged without incubation, resuspended, and observed for agglutination with the naked eye. To each tube assessed by Sal-IS, two drops of 20% polyethylene-glycol (PEG) enhancing reagent, prepared in house [2] were added. After incubating at 37 °C for 15 minutes, samples were washed four times with saline, and two drops of anti-human IgG reagent (Ortho Anti-IgG, rabbit)

were added for PEG-enhanced indirect-antiglobulin testing (PEG-IAT). One drop of in-house IgG-coated RBCs were added to each negative tube, and examined after centrifugation to rule out falsely negative agglutination. Screening specimens were obtained within seven days prior to transfusion and at any time after transfusion.

Immunogenicity of blood group antigens

For immunogenicity calculations, we used previously published antigen frequencies for the Japanese population [10]. Naturally occurring or cold-reactive antibodies (reactive only at room temperature by Sal-IS) and autoantibodies were excluded. Calculations for D antigen were omitted because RBC transfusions have been matched for D negative patients for over 70 years. Preexisting antibodies detected at initial antibody screen were included for the immunogenicity calculations, using the coefficients of total fractional antibody persistence rates, preexisting and hospital-acquired, as reported previously in a Caucasian-dominant population [6, 7].

For immunogenicity calculations, we adopted 4-RBC donor transfusion exposure based on the mean number (4.2) of transfused RBCs observed in this current study. A Japanese “unit” of transfusion is based historically on 200 mL whole blood donations, although 400 mL whole blood donations are now common. Thus, number of donors was used in this study instead of number of units. The original Giblett’s immunogenicity calculation is made in a transfused population: the probability of antigen exposure via single RBC transfusions to the antigen negative recipients, i.e., $Ag_x \text{ positive} \times Ag_x \text{ negative}$ [4]. For multiple-unit transfusion, the fractional probability of an antigen-positive RBC increases from $[1 - Ag_x \text{ neg}]$ or $[Ag_x \text{ pos}]$ to $[1 - (Ag_x \text{ neg})^{\text{number of bags}}]$, where $Ag_x \text{ neg}$ represents the expected fraction of RBC bag negative for the antigen (Ag_x) in the study population, as shown in Figure 1 [8].

Statistical analysis

All statistical analyses were conducted with Stat Mate IV for Microsoft Windows, version 4.01 (ATMS, Niigata, Japan). To analyze the difference of alloimmunization rates, values were expressed as a proportion and compared with the chi-square test and 95% confidence interval (CI). Results were deemed to be statistically significant if the 95% CI did not contain its reference value, which is equivalent to a p-value of <0.05 .

RESULTS

Alloantibody detection rates

Alloantibodies reactive by IAT were detected in 1.28% (638/49,884) of recipients after transfusion, as shown in Figure 2. There was a statistically significant difference ($p < 0.001$) of antibody detection rates between recipients

who were women (1.53%, 391/25,563) versus men (1.02%, 247/24,321). Anti-Jr^a was predominantly found among women (35.2/100,000, 95% CI: 12.2–58.2) compared to men (4.1/100,000, 95% CI: 0.1–22.9), albeit without statistical significance.

$$\text{Immunogenicity of Ag}_x = \frac{\text{Observed number of anti-Ag}_x}{[1 - (\text{Ag}_{x,\text{neg}})^{\text{mean RBC bags transfused}}] \times [\text{Ag}_{x,\text{neg}}] \times [\text{fractional persistence of anti-Ag}_x] \times [\text{number of male recipients}]}$$

Anti-Ag_x: Antibody directed against antigen X; Ag_{x,neg}: Fraction of individuals who are Ag_x negative.

Figure 1: The modified immunogenicity calculation that corrects for the mean number of red blood cell bags transfused per recipient.

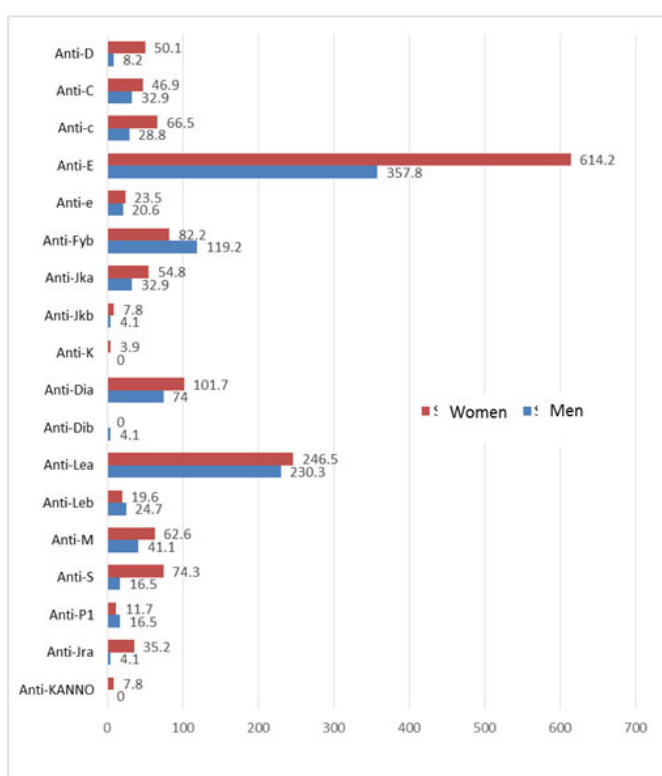


Figure 2: Frequencies of alloantibodies against red cell antigens.

Immunogenicity of red cell antigens in males

Antigen immunogenicity calculations were made with the formula shown in Figure 1 and a mean transfused RBC donor exposure of 4. As shown in Table 1, with antigen potency corrected for antibody persistence, we found that Jr^a was possibly the most immunogenic antigens (>60/1000 per 4 donor exposures). We also found Le^a and Di^b to be highly immunogenic (>20/1000), followed by E and Jk^a (ranging 11.9–5.7/1000). Furthermore, antigenic potency rankings, derived from the fraction of antibody-producing recipients, adjusted for the incidence of antibody negativity in Japanese male cohorts overall,

under the assumption of 4- donor exposures via RBC transfusion were: Jr^a(67.4, 95% CI: 1.7–323.3), >Le^a(23.5, 95% CI: 17.4–29.6), >Di^b(20.1, 95% CI: 0.5–109.3), >E(11.9, 95% CI: 9.4–14.4), >Jk^a(5.7, 95% CI: 1.7–9.6), >Le^b(4.5, 95% CI: 0.9–8.2), >M(2.8, 95% CI: 1.1–4.5), >C(2.5, 95% CI: 1.1–5.0), =Fy^b(2.5, 95% CI: 1.6–3.5), =Di^a(2.5, 95% CI: 1.5–4.0), >e(2.1, 95% CI: 0.3–3.9), >c(1.0, 95% CI: 0.2–1.7), and >S(0.7, 95% CI: 0.2–1.8).

DISCUSSION

By introducing immediate spin instead of 10-minute incubation in saline, omitting the Bromeline stage of testing, and using PEG instead of albumin in IAT, the detection rates of clinically significant antibodies including anti-E, anti-Fy^b, anti-Jk^a, and anti-Jk^b increased, while those of clinically insignificant cold-reactive anti-Le^b and anti-P1 decreased [11]. It has been argued that cold-reactive antibodies like anti-Le^a/Le^b and anti-P1 can be ignored when selecting “compatible” RBCs [12, 13], although if warm-reactive, then consideration should be given to providing units negative for these antigens as well [13].

We excluded female recipients to avoid pregnancy-related alloimmunization which would confound the calculation of transfusion-related alloimmunization. As we did not include details of age, disease, or patient/disorder related factors in our cohort, results reported in this study may also be influenced by other variables. Diseases and treatments of transfusion recipients have been reported to be factors of importance in red cell alloimmunization [14–17]. Universal leukoreduction, adopted throughout Japan in February 2007, is reported to have little impact on red cell alloimmunization following transfusion [1, 18], leading us to believe that leukoreduction is not a confounding variable in our study. The 1.28% of overall alloimmunization rate among Japanese recipients is lower than in Caucasian-dominant populations. Even without statistical significance, anti-Jr^a was found more frequently among women than men, suggesting that pregnancy may be its main route for alloimmunization [19]; this is plausible because the antigen is also expressed on fetus-origin chorionic tissue of the placenta [20]. Higher than other ethnic populations, Jr(a-) individuals account for 0.06% of Japanese. Moreover, almost all Jr(a-) phenotypes arise from several null alleles of the ABCG2 transporter gene, rather than single-nucleotide polymorphisms [21]; thus Jr(a-) individuals recognize Jr^a antigen frequently in an iso-immune manner rather than alloimmune recognition.

In this Japanese survey, the relative potencies of strong antigens (E > Jk^a) resembled partly those of Caucasians (K > Lu^a > E > Jk^a) [7], and were comparable among other antigens (C, c, P1, Le^a, Le^b, and M). However, it was impossible to compare the immunogenicity of K, Lu^a, and C^w, because no one in our male cohort had antibodies against these antigens. Further, we found that

Table 1: Probability of exposure to individual antigens via a transfusion and comparison of the immunogenicities of blood group alloantigens

Antigen	Antigen frequency positive/negative (Japanese population)	Traditional probability of stimulating the antibody formation*	Fractional persistence rate**	Number of estimated potency recipients of red cell antigen, traditional/corrected (1 donor)/ (4 donors)***	Antibodies reactive at IAT phase	Ratios of antibody-produced recipients per corrected candidates (4 donors) (per 1000) [95% CI]
D	0.995/0.005				2	
C	0.85/0.15	0.1275	0.864	3101/2679/3150	8	2.5 [1.1–5.0]
c	0.55/0.45	0.2475	0.700	6019/4213/7346	7	1.0 [0.2–1.7]
E	0.5/0.5	0.25	0.642	6080/3903/7319	87	11.9 [9.4–14.4]
e	0.9/0.1	0.09	1.000	2189/2189/2432	5	2.1 [0.3–3.9]
Fy ^a	0.99/0.01	0.0099	0.750	241/181/182	0	0.0 [0.0–20.2]
Fy ^b	0.196/0.804	0.157584	1.000	3833/3833/11383	29	2.5 [1.6–3.5]
Jk ^a	0.728/0.272	0.198016	0.214	4816/1031/1407	8	5.7 [1.7–9.6]
Jk ^b	0.776/0.224	0.173824	1.000	4268/4268/5434	1	0.2 [0.0–1.0]
K	0.0003/0.9997	0.00030	0.646	7.3/4.7/18.8	0	0 [0–178.4]
Di ^a	0.092/0.908	0.08354	Not available	2032/Not available/7072	18	2.5 [1.5–4.0]****
Di ^b	0.998/0.002	0.001996	Not available	49/Not available/49	1	20.1 [0.5–109.3]****
Le ^a	0.83/0.17	0.1411	0.577	3432/1980/2384	56	23.5 [17.4–29.6]
Le ^b	0.898/0.102	0.091596	0.533	2228/1186/1322	6	4.5 [0.9–8.2]
M	0.777/0.223	0.173271	0.667	4214/2811/3609	10	2.8 [1.1–4.5]
S	0.112/0.888	0.099456	1.000	2419/2419/5832	4	0.7 [0.2–1.8]
P1	0.31/0.69	0.2139	0.500	5202/1070/6489	4	0.6 [0.2–1.6]
Jr ^a	0.99939/0.00061	0.00061	Not available	14.8/Not available/14.8	1	67.4 [1.7–323.3]****

*Probability of antigen exposure was calculated as antigen negative × antigen positive [4].

**Fractional persistence rate represent the ratio of lasting antibodies of the total antibodies of that specificity, as calculated by Tormey and Stack [6].

***Corrected numbers of traditional antigen potency [4] × fractional persistence ratio [7] × male recipients (24,321).

****Fractional persistence 1.0 was used.

Di^b was highly antigenic, however, Diego incompatibility in pregnancy and transfusion is predominantly found among Asians and Native Americans [22], so we could not compare it with Caucasian data.

As a limitation, the number of antibody positive cases of anti-Jk^b, anti-Di^b, and anti-Jr^a were so small that the 95% CI were so wide, and thus the statistical significance lacked power. Next, we applied evanescence/persistence rates determined from Caucasian populations. Although there is currently no data that these rates among Japanese are similar

to Caucasians, immunogenicity based on other ethnic groups' estimates may be necessary until more data are gathered. Furthermore, antibody screening performed at any time following transfusion may introduce biases of antibody specificity [18].

CONCLUSION

In summary, using the sensitive and accurate antibody identification steps, we were for the first time

able to estimate blood group antigen immunogenicity in a Japanese population. Jr^a and Diego blood group antigens, not previously assessed in Caucasian cohorts, might be highly immunogenic in the Japanese population. Confirmation of this hypothesis would require a larger cohort of patients.

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Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Informed consent was obtained and documented for the collection and analysis of all patient-related data used in this study.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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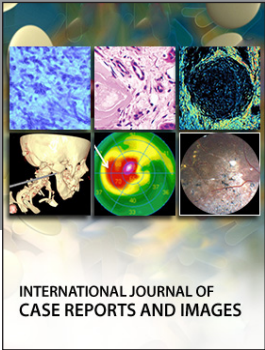
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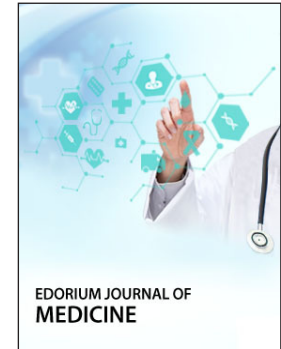
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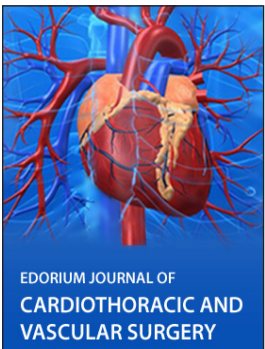
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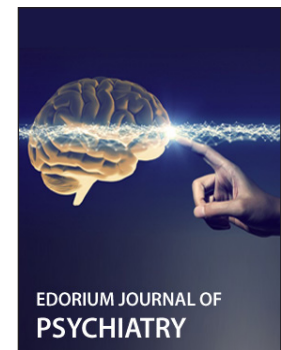
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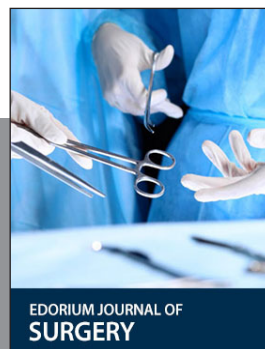
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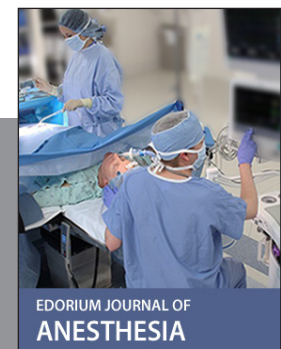
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