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Low incidence of anti-D alloimmunization following D+ platelet transfusion: The Anti-D Alloimmunization after D-incompatible Platelet Transfusions (ADAPT) study

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Summary

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Authorship

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The reported frequency of D alloimmunization in D- recipients after transfusion of D+ platelets varies. This study was designed to determine the frequency of D alloimmunization, previously reported to be an average of 5%±2%. A primary anti-D immune response was defined as the detection of anti-D ≥28 days following the first D+ platelet transfusion. Data were collected on 485 D- recipients of D+ platelets in 11 centres between 2010-2012. Their median age was 60 (range 2-100) years. Diagnoses included: haematological (203/485, 42%), oncological (64/485, 13%) and other diseases (218/485, 45%). Only 7/485 (1.44%; 95%CI 0.58-2.97%) recipients had a primary anti-D response after a median serological follow-up of 77 days (range: 28-2111). There were no statistically significant differences between the primary anti-D formers and the other patients, in terms of gender, age, receipt of immunosuppressive therapy, proportion of patients with haematological/oncological diseases, transfusion of whole blood-derived or apheresis platelets or both, and total number of transfused platelet products. This is the largest study with the longest follow-up of D alloimmunization following D+ platelet transfusion. The low frequency of D alloimmunization should be considered when deciding whether to administer Rh Immune Globulin to D- males and D- females without childbearing potential after transfusion of D+ platelets.

Keywords

platelet transfusion; D compatibility; anti-D alloantibodies; alloimmunization; RhIG

Introduction

Unlike ABO antigens, Rh antigens are not expressed on the platelet membrane (Dunstan *et al*, 1984). However, platelet concentrates (PC) are still labelled for transfusion by the D status of the donor because of the presence of very small quantities of D+ red blood cells (RBCs) in the PC unit (European Committee on Blood Transfusion, 2010). These accompanying D+ RBCs have been reported to have caused D alloimmunization in up to 19% of D- recipients (Lozano & Cid, 2003), although a careful re-analysis of the data in these studies suggests that this frequency could be lower than 7% (Cid *et al*, 2013). The presence of anti-D (D alloantibodies) can have a severe impact on D+ fetuses, and it limits the recipient's ability to receive D+ RBCs in times of D- RBC shortage. Therefore, current guidelines recommend that D- recipients, particularly women of childbearing age, should receive PCs from D- donors (Association of American Blood Banks [AABB], 2012; European Committee on Blood Transfusion, 2010). If platelets obtained from D+ donors are transfused to females of childbearing potential, it is recommended that Rh Immune Globulin (RhIG) should be given to reduce the risk of alloimmunization (AABB, 2012; European Committee on Blood Transfusion, 2010). RhIG is a human sourced product that has undergone a variety of pathogen inactivation procedures and is becoming increasingly scarce around the world. However, these recommendations are based on limited evidence from studies with small numbers of patients and limited follow-up (Menitove, 2002), and an optimal approach to the use of RhIG has not been identified (Ayache & Herman, 2008). To help inform decisions on RhIG administration, the Biomedical Excellence for Safer Transfusion (BEST) Collaborative designed an international, retrospective study to collect

data from D- patients who received D+ PC transfusions from 11 centres in 5 countries in order to determine the frequency of D alloimmunization.

Methods

Patients

Transfusion service members of the BEST collaborative and invited collaborators were asked to participate in this retrospective study. Participating sites searched their electronic databases for D- recipients of D+ PCs during the 3 calendar years from 2010, 2011 and 2012. Each participating site used their standard reagents and platforms for D typing and assigned the recipient's D status according to their local policies at the time of testing. The first D+ PC that the recipient received at each site during the study period was defined as the index D+ platelet transfusion.

Patients were eligible for the study if they were D-, were not known to have anti-D before receiving the index D+ PC, had no previous exposure to D+ blood components and had an antibody screen performed at least 28 days after receiving the index D+ PC. D- recipients with any underlying disease who met these criteria were included. Patients were excluded if there was documentary evidence that they received RhIG following any D+ platelet transfusion, had a previously identified D alloantibody, were a recipient of D+ RBCs or D+ platelets before 2010, or received D+ RBCs either before or after the index D+ platelet transfusion during the study period.

Collected data

The following variables were collected from medical record of each patient: gender, age, ABO and Rh(D) group, main diagnosis (haematological, oncological, other), previous transfusion history and previous pregnancies (if applicable and/or available). Information regarding the platelet products transfused during the period of study was obtained by collecting the following variables from electronic databases: the total number of PCs issued, the type of PC (whole blood-derived or apheresis), the ABO compatibility or not (major, minor, or mixed incompatibility) and the Rh(D) compatibility of each unit.The following information was collected regarding serological follow-up: the result of the antibody screen performed at the time of the index D+ platelet transfusion, and the result of the last antibody screen performed. The length of serological follow-up was also recorded; this is the number of days that elapsed between the index D+ platelet transfusion and either the date of the last recorded negative antibody screen or the detection of anti-D.

As the literature supports a 28-day minimum period to produce a primary anti-D immune response, any D alloantibodies detected within 27 days of the index D+ platelet transfusion were defined as secondary immune responses, i.e., anamnestic immune responses (Lozano & Cid, 2003). These recipients were not enumerated amongst those who produced a primary anti-D immune response (i.e., anti-D detected ≥28 days after the index D+ platelet transfusion). Where required, the Research Ethics Committees (Hospital Clínic, Barcelona, Spain) or Institutional Review Boards at each of the participating sites (Beth Israel

Deaconess Medical Centre, Boston, MA; University of Washington, Seattle, WA; and UCLA, Los Angeles, CA) approved this protocol.

Statistical analysis

The sample size was based on the D alloimmunization frequencies that had been previously reported. On average, the cited alloimmunization frequency is 5%±2%. Thus, in order to establish with 95% confidence that the actual alloimmunization frequency is between 3% and 7%, it was calculated that 456 patients would have to be included in this study. The 95% confidence interval (CI) surrounding the frequency of D alloimmunization was determined according to the 2-sided Poisson distribution. The differences between dichotomous variables were compared using the Fisher's exact test. Differences in continuous variables were compared using the Mann-Whitney U test. $P < 0.05$ was considered statistically significant. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Software, release 19.0, IBM Corporation, Armonk, NY).

Results

In total, 11 centres from 5 countries contributed data to this study. A total of 485 recipients were analysed; 224 (46%) from European centres and 261 (54%) from centres in the Americas. Forty-eight of the 485 (9.9%) patients included in this study had been previously studied and reported (O'Brien *et al*, 2014). The demographic data of these recipients are presented in Table I. Of the 182 females, 57 (31%) had a prior pregnancy and 12 (7%) had not been pregnant. A pregnancy history was not available for the remaining 113 (62%) female recipients.

The antibody screen result at the time of the D+ index platelet transfusion was not available in 33/485 (7%) of the recipients. Of the other 452 patients, the antibody screen was negative in 447 (99%) recipients, while 5 recipients had RBC antibodies: anti-K (n=2), anti-Jk^a (n=1), anti-Fy^a (n=1) and a warm autoantibody (n=1).

The type and quantity of the platelets transfused to the recipients in this study are presented in Table II.

After a median serological follow-up of 77 days (range: 28-2111), 21 (4.3%) patients had developed a new RBC antibody: anti-D (n=11), anti-Jk^a (n=4), anti-E (n=2), warm autoantibody (n=2), anti-K (n=1), anti-Fy^a (n=1). Of the 11 recipients in who anti-D was detected, 4 patients had their anti-D detected 13, 15, 21, and 24 days after receiving the D+ index platelet transfusion. The other 7 patients who formed anti-D had their anti-D antibodies detected after a median of 216 days (range: 32-368) following the D+ index platelet transfusion. Of the 4 patients whose anti-D was detected <28 days following the index platelet transfusion, none had a pre-existing RBC antibody. Of the other 7 patients, 1 (14%) had a pre-existing RBC antibody. Thus the frequency of primary D alloimmunization in this study was 7/485 (1.44%; 95% CI: 0.58-2.97%).

Table III demonstrates the demographic and clinical data of the recipients who produced a primary anti-D and those who did not produce a primary anti-D (the latter group included

the 4 recipients whose anti-D was detected <28 days after the index transfusion). There were no significant differences noted between the 7 primary anti-D formers and the other recipients in this study in any of the parameters analysed. Table IV demonstrates the number of PC units transfused to the primary alloimmunized recipients vs. all others in this study. There was no significant difference in the number of D+ or D- PC units administered between these 2 groups of recipients. There were also no significant differences in ABO-compatibility between the D+ and D- PC units administered to these 2 groups of recipients.

Discussion

This is the largest study of the frequency of D alloimmunization amongst D- recipients of D + PC transfusions. The frequency of D alloimmunization in this study was 1.44%. Important strengths of this study were that it did not exclude recipients based on their diagnosis and it reflected the experience of 11 centres around the world.

In studies published before 2000, the incidence of D alloimmunization in D- recipients after receiving D+ PC transfusions was reported to be up to 19% (Goldfinger & McGinniss, 1971; Lichtiger *et al*, 1983; Baldwin *et al*, 1988; McLeod *et al*, 1990; Heim *et al*, 1992; Zeiler *et al*, 1994). However, data from more recent studies reported either a zero or a very low frequency of D alloimmunization following D+ PC transfusion (Atoyebi *et al*, 2000; Molnar *et al*, 2002; Cid *et al*, 2002; Cid, 2003; Misso *et al*, 2006; Bartley *et al*, 2009; Cid *et al*, 2011; Moncharmont *et al*, 2014; O'Brien *et al*, 2014). Thus, the findings of this study confirm the more recently reported lower frequency of D alloimmunization.

There are 3 explanations for the low D alloimmunization frequency determined in this study. First, the RBC content in the transfused PCs was very low (Cid & Lozano, 2005). While the RBC content of each PC that was transfused during the study period was not quantified, quality control data from the participating centres indicated that the mean RBC content in PCs prepared from whole blood collections or obtained from apheresis devices was only 0.036 ml and 0.00043 ml, respectively (http://www.bancsang.net/en/professionals/resum_qualitat.html, last accessed 2 June 2014). These data, regarding the RBC content in PCs, are consistent with previous reports (Santana & Dumont, 2006; Culibrk *et al*, 2012). There is evidence that the minimum RBC volume necessary to elicit a primary anti-D immune response is only 0.03 ml (Lozano & Cid, 2003), which is within the range of the quality control data from the centres in this study that transfused PCs prepared from whole blood collections. However, there was no difference in the type of PC product (apheresis vs. whole blood derived platelets) transfused between the 7 primary anti-D formers and the rest of the cohort. In this recipient population, composed mainly of haematology/oncology patients, the small quantity of RBCs did not provoke an alloimmune response.

Second, the level of immunosuppression plays a role in developing anti-D. (Klein & Anstee, 2005). Data are derived from observations of D- volunteers systematically and repeatedly immunized with small quantities of D+ RBCs indicate that the frequency of D alloimmunization is greater than 80% following incompatible RBC transfusions in immunocompetent individuals. However, even after receiving D+ RBC units, immunosuppressed patients, such as haematopoietic progenitor cell transplantation

recipients (Cid *et al*, 2006; Cid *et al*, 2014), HIV-infected patients (Boctor *et al*, 2003) and solid organ transplantation recipients (Yuan *et al*, 2008), did not develop anti-D. Moreover, retrospective or prospective studies of hospitalized D- patients who were not on immunosuppressive medications demonstrated D alloimmunization frequencies of around 20% after receipt of at least 1 unit of D+ RBCs (Frohn *et al*, 2003; Yazer & Triulzi, 2007; Gonzalez-Porras *et al*, 2008). This frequency is between the 80% cited above and the 1.44% frequency observed in this study, although closer to the latter. It has been suggested that this lower frequency of D alloimmunization amongst hospitalized patients could be attributed to stress-induced immune suppression (Frohn *et al*, 2003). Thus given the small quantity of RBCs in modern PCs and the potential for stress-induced immunosuppression (with or without iatrogenic immunosuppressive therapy), it is not surprising that the frequency of D alloimmunization following D+ PC transfusion is very low.

Third, to elucidate the true frequency of primary D alloimmunization in D- recipients of D+ PCs, it is important to exclude those who might demonstrate a secondary immune response when transfused with D+ blood products again. It is known that the earliest time at which anti-D can be detected in a primary immunization scenario in immunocompetent individuals ranges from 4 to 10 weeks following the D+ transfusion, with the production of anti-D within 2 weeks of a first D+ stimulus observed only after the injection of specially treated D + RBCs (Gunson *et al*, 1971). The frequency of D alloimmunization in several previous studies could have been confounded by the inclusion of recipients who demonstrated a secondary, not primary, immune response to D+ PCs (Goldfinger & McGinniss, 1971; Baldwin *et al*, 1988; McLeod *et al*, 1990). For this reason, the present study defined a primary D alloimmunization event as one in which the anti-D was detected ≥28 days after receiving the D+ index platelet transfusion. Despite this definition, it is still theoretically possible that the 2 patients who had their anti-D detected at 21 and 24 days post-index transfusion were having a primary response. This would slightly increase the overall alloimmunization rate to 9/485 (1.86%). To minimize the chances of including a patient who could have demonstrated a secondary immune response to the D antigen, patients who had received D+ blood products before 2010 were excluded, as were those who received D+ RBCs during the study period. The latter exclusion criteria also ensured that any primary D alloimmunization that occurred during the study period was due to the index D+ PC transfusion and not a D+ RBC transfusion.

This study has some limitations. Because it was a retrospective study and the recipients' antibody screens were not serially followed, the exact time frame in which the 11 recipients formed their primary anti-D cannot be determined. It can only be shown that these recipients became alloimmunized, not when it occurred. Thus it is possible that some of the recipients whose anti-D was detected ≥28 days after the index D+ platelet transfusion might have actually produced it within 27 days of the index transfusion; if this was the case then the frequency of primary anti-D formation would be lower than 1.44% as there would be fewer primary alloimmunized recipients. Data on the continued presence of these new anti-D antibodies after their detection was not collected and so it is not possible to determine if these antibodies evanesced. However, data from previous studies suggest that the frequency of evanescence of D alloantibodies varies between 5.56% (Tormey & Stack, 2009) and 13%

(Schonewille *et al*, 2000) and that antibody loss occurs after 0.1-5 years (Ramsey & Larson, 1988) or >5 years (Ramsey & Smietana, 1994). As the D antigen detection techniques varied between the 11 participating centres, it is also possible that variability in assigning the recipients' D status between centres might have confounded these results, i.e., a centre using a low-sensitivity D typing reagent or platform would be more likely to have more D- recipients than a different centre using higher sensitivity testing methods. Whether many of these so called weak D recipients are at risk of alloimmunization is a matter of debate, but if they are not predisposed to D alloimmunization at the same frequency as truly D- recipients, then including weak D recipients in this study would artificially reduce the alloimmunization frequency. As none of the D- recipients underwent *RHD* genotyping, the true number of weak D recipients amongst these 485 recipients is unknown but is likely to be low. Similarly, differences in anti-D detection methods between the 11 participating centres would also confound the true alloimmunization frequency, favouring the sites that use more sensitive methods. Furthermore, although every effort was made to exclude recipients who had received D+ RBCs and platelets before the index platelet transfusion, or D+ RBCs during the study period, it is possible that the recipients might have been transfused with D+ products at other centres, thus confounding their inclusion in this study. Whether tolerance to the D antigen developed as a result of these hypothetical D+ transfusions is unknown, although the more recipients with D tolerance that were unknowingly included in the study, the more the alloimmunization frequency would have been artificially decreased as they would not have been susceptible to producing anti-D following the D+ PC transfusions. That 4 recipients demonstrated a secondary immune response to D following the index D+ PC transfusion despite having no record of historical D+ PC or RBC transfusion suggests that indeed some patients had been transfused elsewhere with D+ products. Lastly, with longer serological follow-up periods, it is possible that anti-D would have been detected in more recipients, particularly as these patients were not serially followed with antibody screens. It was interesting that there were no demographic or clinical differences found between those who demonstrated a primary anti-D immune response and those who did not. This indicates that the propensity for alloimmunization probably depends on subtle differences in the recipient's immune and inflammatory statuses that are not represented in the parameters collected in this study.

In conclusion, this Anti-D Alloimmunization after D-incompatible Platelet Transfusions (ADAPT) study analysed the largest number of D- recipients of D+ PCs with a variety of diagnoses and, with the longest median serological follow-up period published to date, demonstrated that the frequency of D alloimmunization in this clinical scenario was 1.44%. The low frequency of D alloimmunization should be considered when deciding whether to administer RhIG to D- males and D- women without childbearing potential who received D + platelets.

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Table I

Demographics of the recipients in this study. There were 485 recipients of platelet concentrates in this study. Data are presented as the number of recipients (% of total) or median (range).

Parameter	Demographics
Gender (male/female)	303 (62%) / 182 (38%)
Age (years)	60 (2-100)
Main diagnosis (haematological/oncological/other)	203 (42%) / 64 (13%) / 218 (45%)
Previous transfusions (RBC, PC)	222 (46%) / 95 (20%)
Immunosuppression (yes/no)*	200 (53%) / 180 (47%)
ABO group (O/A/B/AB)	209 (43%) / 215 (44%) / 44 (9%) / 17 (4%)

RBC, red blood cell; PC, platelet concentrate.

* Information available for 380 recipients

Table II

Type and quantity of the platelets transfused to the 485 recipients in this study.

Platelet product type	D+ (n)	D- (n)	Total (n)
Whole blood-derived platelets	1180	1505	2685
Apheresis platelets	1970	694	2664
Total number	3150	2199	5349

Table III

Demographic and clinical information of the primary alloimmunized recipients vs. all other recipients in this study.

Parameter	Primary anti-D formers	All other recipients	p value
Number of recipients (%)	7 (1.4)	478 (98.6)	NC
Gender (Male/Female)	4/3	299/179	0.2
Median age (range), years	60 (2-100)	65 (39-85)	0.2
ABO group (O/A/B/AB)	3/3/1/0	206/212/43/17	0.9
Main diagnosis (haematology-oncology/others)	3/4	264/214	0.5
Iatrogenic immunosuppression (yes/no/unknown)	3/3/1	197/177/104	0.9
History of pregnancy (yes/no)*	2/0	55/12	0.5
Patient location: Europe/Americas	2/5	222/256	0.6
Previous RBC transfusion (yes/no)	6/1	217/261	0.08
Previous PC transfusion (yes/no)	2/5	94/384	0.9
Transfused PCs (whole blood/apheresis/both)	2/4/1	179/288/71	0.8
Median length of serological follow-up (range), days	216 (32-368)	75 (28-2111)	0.09

RBC, red blood cell; PC, platelet concentrate; NC, Not calculated

*For those whose pregnancy history was known

Table IV

Number of platelet concentrate units administered to those who produced a primary anti-D and those who did not. Data are presented as median (range) unless otherwise specified.

Parameter	Primary anti-D formers	All other recipients	p value
Recipients, n (% of total)	7 (1.4)	478 (98.6)	NC
D+ PC	2 (1-31)	2 (1-115)	0.9
D- PC	0 (0-14)	0 (0-127)	0.5
Total PC	2 (1-37)	3 (1-157)	0.5

PC, platelet concentrate; NC, Not calculated