

Elimination of pretransfusion RhD typing at Mackay Memorial Hospital, Taiwan—30-year experience (1988–2017)

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Vox Sanguinis

Background The frequency of the RhD negative (D-) phenotype among the population of Taiwan is only 0.34% and so anti-D is a relatively rare antibody. Routine pretransfusion D typing of patients at Mackay Memorial Hospital (MMH) was discontinued in 1988, and this report is a look back and retrospective evaluation over 30-years (1988–2017).

Study Design and Methods The incidence of anti-D among patients at MMH during the periods 1984–1988 (when D typing was performed) and 1988–2017 (when D typing was not performed) was reviewed. Also, the incidence of anti-D among both MMH patients and voluntary blood donors at the Taiwan Blood Foundation was compared. The importance of anti-‘Mi^a’ in Taiwan is also discussed.

Results The incidence of anti-D relative to other Rh antibodies among MMH patients when D typing was performed and D typing not performed has remained relatively unchanged (5%). The frequencies of anti-D and anti-‘Mi^a’ among 38 537 patients who were transfused at MMH during 2008–2017 were found to be 0.06% and 2.6%, respectively. During the same period, among 3 510 131 blood donors at Taiwan Blood Foundation, the frequencies of anti-D and anti-‘Mi^a’ were 0.004% and 0.2%, respectively.

Conclusion The elimination of D typing of patients at MMH has proven to have been a correct and logical decision. D- patients, if they do not carry anti-D, can thus be safely transfused with D+ red cells.

Key words: anti-‘Mi^a’, anti-D, anti-D induced by the D_{el} phenotype, blood transfusion in D-, Taiwan.

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Introduction

Modification of ‘standard Western pretransfusion testing’ for use in Taiwan [1] has been a difficult task, as it is considered the global gold standard. However, for the past 30 years, (since 1988) MMH has not routinely performed D typing of patients requiring transfusion because 99.66% of the population of Taiwan are D+. Prior to 1988, undertransfusion of D- patients often occurred because D- blood was often unavailable due to blood

donation being still in its infancy, resulting in several fatal outcomes, especially in emergency situations. In 1988, MMH made the courageous decision to discontinue routine pretransfusion D typing of patients in order to reduce the fear surrounding the D- phenotype among Taiwan’s general population and also to help inform medical personnel that transfusing D+ blood to D- patients who did not carry anti-D was safe. In addition, Prof. M. Contreras of the North London Blood Centre replied to our letter of concern as follows: ‘After a long discussion with Prof. Mollison... it is not logical to type for D when E-typing and c-typing are not done... My conscience is quite clear when I give you this advice that it is ethical to discontinue routine Rh(D) typing of recipients and

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antenatal patients'. (Contreras, personal communication, 1985). In addition, at that time we were trying to save limited medical resources by eliminating unnecessary testing (National Health Insurance was established in 1995 and offered reimbursement to hospitals for D typing). From 1988–2018, pretransfusion testing at MMH consisted of ABO grouping, antibody screening and major cross-matching by the manual Polybrene method. No D typing was performed [1,2]. MMH is a general hospital and also a teaching medical centre with 1130 beds, usually having 90% bed occupancy rate. During 2008–2017, 30 000–32 000 units of RBC were transfused each year (every unit was made from 250 ml whole blood). The Taiwan blood donation centre usually delivers only D+ blood to hospitals if there is no special request for D– blood. On the other hand, RhD typing is a routine test in the prenatal care of our Obstetric Department for any female patient who wants to have a baby.

This report is a look back evaluation of our policy to discontinue D typing over the past 30 years by analysing the incidence of anti-D among both patients and blood donors. However, it is of interest to mention that at the end of 2018, the blood bank at MMH started to automate and D typing was reintroduced due to the purchase of a Western style analyser which included both ABO and D typing reagents together. In addition, Taiwan has in recent years gradually become a global village and many Caucasians now live in Taiwan. Therefore, since the end of 2018, D typing has once again become part of the routine pretransfusion testing protocol at MMH. However, we hope that our 30 years' experience might be helpful to other Southeast Asian countries whose populations are genetically closely related to Taiwan and also have a high incidence of both D and 'Mi^a' (Miltenberger) phenotypes [3,4].

Materials and methods

The incidence of anti-D among patients at MMH during the periods 1984–1988 (D typing performed) and 1988–2017 (D typing not performed) was reviewed. In addition, the incidence of anti-D in both patients (MMH) and blood donors (Taiwan Blood Foundation) [5] was compared. The clinical significance of both anti-D and anti-'Mi^a' (the most common alloantibody in Taiwan) among both patients and blood donors was also analysed.

Results

From Table 1, it can be seen that the relative frequency of anti-D vs. other Rh system alloantibodies (5%) among hospital patients at MMH has remained unchanged whether D typing was performed routinely (1984–1988)

or not performed (1988–2017). In fact, it actually decreased to 2% during the most recent 10-years period (2008–2017). A similar result (5%) was observed among blood donors and interestingly was obtained during the period when all hospitals in Taiwan, except MMH, were all routinely performing pretransfusion D typing of patients.

From Table 2, it can be seen that during the period 2008–2017 among 38 537 patients at MMH, 1002 cases of anti-'Mi^a' (2.6%) were detected compared with only 22 cases of anti-D (0.06%) [6]. During the same period among 3 510 131 blood donors at Taiwan Blood Foundation, 7015 cases of anti-'Mi^a' (0.2%) were detected compared with only 146 cases of anti-D (0.004%) [5] indicating that anti-D is a relatively low-frequency alloantibody compared with other clinically significant alloantibodies. See the complete list of alloantibodies in Table 2.

Among 22 D– patients who had anti-D during 2008–2017 at MMH, 10 cases were induced by transfusion (Table 3): nine cases were the result of transfusion of D+ blood and one case was due to the transfusion of 2 units of the D_{el} phenotype. This latter case occurred in an 81-year-old lady with upper G-I bleeding. Anti-D was detected 3 months after the transfusion of 4 units of D– blood and 2 units of D_{el} positive blood. Of the remaining 12 D– patients with anti-D, 10 patients had all been previously sensitized prior to transfusion at MMH; one patient had passively received anti-D from transfusion of D– blood carrying anti-D and one patient due to Rhogam administration. During the 10-year period from July 1992 to June 2002, five cases of transfusion-induced anti-D occurred at MMH [7].

Since anti-'Mi^a' and anti-E are the most common alloantibodies detected among patients at MMH, it is not surprising to discover that anti-E/E+c and anti-'Mi^a' are also commonly incriminated in haemolytic disease of the newborn (HDNB). During the period 2008–2017 at MMH, the causative antibodies of HDNB were found to be anti-E/E+c (16 cases), anti-Jk^b (three cases), anti-'Mi^a/'Mi^a+E (two cases) and one case each of anti-C+ e and anti-D. Not surprisingly, anti-D rarely causes HDNB among Taiwanese.

Discussion

The D– phenotype is rare among the population of Taiwan with a frequency of 0.34% (Taiwan Blood Foundation). Since the discontinuation of routine pretransfusion D typing of patients at MMH 30 years ago, it is likely that almost all D– patients since then have been transfused with D+ blood. However, the incidence of anti-D did not increase during this period and has actually decreased

Table 1 Comparison of the incidence of anti-D vs. other Rh system alloantibodies among MMH patients, before (1984–1988) and after (1988–2017) discontinuation of routine pretransfusion D typing, with that among blood donors

Year	Routine D typing	Number of cases of anti-D vs. other Rh system alloantibodies	%
1984–1988 ^a [4]	Yes	5/103	5
1992–1996 ^a [4]	No	4/102	4
1999–2001 ^a [4]	No	10/194	5
2008–2017 ^a [4]	No	22/1404	2
2008–2017 [5](blood donors)	Yes	146/2792	5

^aPatients at MMH.**Table 2** Alloantibodies encountered during the most recent 10 years (2008–2017) in patients at MMH and among blood donors at the Taiwan Blood Foundation

MMH [6] Total no. of patients: 38 537		Taiwan Blood Foundation [5] Total no. of blood donors: 3 510 131	
Anti-	No.	Anti-	No.
'Mi ^a	1002	'Mi ^a	7015
E	906	P1	3159
c	367	Le ^a	2440
P1	257	E	2281
Le ^a	198	Le ^b	1660
M	193	M	1537
C	73	c	283
Le ^b	70	Wr ^a	165
Di ^a	60	D	146
e	58	S	138
Jk ^a	58	e	116
Jk ^b	42	Di ^a	97
Wr ^a	40	C	94
D	22	Fy ^b	43
Fy ^b	19	N	40
S	18	G	13
Bg ^a	16	Jk ^a	8
N	13	Jk ^b	4
Bg ^b	7	Le ^{bh}	4
Fy ^a	1	Jk3	3
Jk3	1	Ce, Cw, Di ^b , M ^g , Pr	2
i	1	V, PP1P ^k , Vw, He, Kp ^a , Ku, Lan, Jr ^a , LW, Lw ^a	1
Total	3422 (8.9%) ^a	Total	19 266 (0.55%) ^a

Antibody screening and identification were performed by the manual Polybrene method at MMH and on an Olympus PK7300 analyser (0.3% bromelinated screening cells on a specially designed microplate) at Taiwan Blood Foundation. Anti-I/HI and cold agglutinins were excluded.

^aFrequency (%) of alloantibodies encountered in patients and blood donors.

during the most recent 10 years (2008–2017), as shown in Table 1. Interestingly, since the discontinuation of routine pretransfusion D typing of hospital patients at MMH, the relative incidence of anti-D versus other Rh alloantibodies (5%) among patients has been found to be identical to that among Taiwanese blood donors (5%) as shown in Table 1. This relative incidence of anti-D versus other Rh alloantibodies among blood donors (3 510 131

donors) is more representative of the actual incidence of anti-D among the general population of Taiwan when all hospitals apart from MMH performed pretransfusion D typing of patients routinely. Therefore, anti-D is not as important in the Taiwan population as it is in Caucasian populations and it appears to be unnecessary to transfuse D- patients in our population with D- blood when they do not carry anti-D.

Table 3 Ten cases of transfusion-induced anti-D detected during 2008–2017 at MMH

Case	Anti-	Sex	Age (year)	Transfused ^a	MP ^b	LIAT
1	D + C+Jk ^a	F	44	2U	3+	4+
2	D + C+E	M	76	4U	3+	3+
3	D + E	F	5M	4U	1+	Negative
4	D	F	92	16U	4+	NA
5	D + E	M	52	2U	1+	±
6	D	F	83	2U	1+	±
7	D	F	81	10U	2+	NA
8 ^c	D	F	81	2U	2+	NA
9	D + C	M	52	5U	1+	NA
10	D	M	38	2U	2+	3+

LIAT, LISS indirect antiglobulin test.

^aUnits of packed RBC transfused.

^bManual Polybrene method.

^cPatient was transfused with 2 units of D_{el} phenotype blood.

With regards to the D_{el} phenotype, as in case 8 in Table 3, it can be seen that transfusing D– patients with ‘supposedly’ D– blood does not necessarily prevent them from producing anti-D due to the presence of the ‘D_{el} phenotype’ [8,9] in the Taiwan population [10]. The D_{el} phenotype is an extremely weak D phenotype in which the D antigen is only detectable by adsorption and elution with anti-D [11] and has a frequency of 32.6% among serologically D– individuals in Taiwan [12]. In case 8, the patient was transfused with 2 units of the D_{el} phenotype resulting in the production of anti-D. The genetic marker *RHD1227A* for the D_{el} phenotype was recently found to be present in all D_{el} individuals [13]. Since 2017, a rapid genotyping assay for the detection of the *RHD1227A* allele is now performed routinely for all D– blood donors (with an additional confirmatory adsorption and elution test with anti-D on all first time D-donors) [14]. The D_{el} phenotype in Taiwan is now considered as D+ and all such units are labelled D+.

In addition, because of the rarity of the D- phenotype in Taiwan it has in the past caused unnecessary anxiety and fear among the general population. This irrational

fear has resulted in significant and harmful under transfusion in many cases. D– patients, if they do not carry anti-D, can thus be safely transfused with D+ red cells.

Since the discovery in 1987 of the GP.Mur phenotype and the corresponding antibody anti-‘Mi^a’ among the Taiwan population, the GP.Mur phenotype has become the clinically most important blood group in Taiwan [12]. The GP.Mur phenotype has therefore been included in antibody screening cells in Taiwan since 1990. In addition, anti-‘Mi^a’ and anti-E have proven to be the most common and clinically significant alloantibodies (see Table 2). Anti-‘Mi^a’ has caused both intravascular haemolytic transfusion reactions and severe HDNB [15,16]. The Taiwan Blood Foundation has successfully produced monoclonal anti-Mi^a, anti-Mur and anti-Mut [17] making it possible to perform mass screening of blood donors. The frequency of the GP.Mur phenotype in Taiwan was found to be 4.71% after the screening of 704 833 donors in 2018 (Taiwan Blood Foundation, 2019).

Since the D- phenotype is rare throughout Southeast Asia, Taiwan’s experience may be of benefit to other countries in this region.

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Conflict of interests

The authors declare no conflict of interests.

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