Alloimmunization against Rh and Kell blood groups antigens is the main obstacle for blood transfusion in transfusion dependent thalassemia patients in Iran

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ABSTRACT

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EDITORIAL

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ALLOIMMUNIZATION IN THALASSEMIA MAJOR

Thalassemia is the most common inherited single-gene disorder, causes by decrease or absence of α -globin or β -globin chain production. The disorder commonly inherited in autosomal recessive manner and is more common in areas with high rate of consanguinity [1–3]. Thalassemia belt is an extensive area which extend from Mediterranean east through Middle-East and India to Southeast Asia and south through Africa. Estimated incidence of thalassemia in this area is varies from 1–20% depend on area. Iran as a Middle-East country with high rate of consanguineous marriage has a considerable number of patients with β -thalassemia major [4–6]. The precise incidence of disorder is not clear in Iran but it was estimated that there are between two and three million beta thalassemia carriers and about 20,000 patients with beta thalassemia major. The main therapeutic choice in these patients is packed red blood cell (pRBC) transfusion. Continuous blood transfusion imposed a number of transfusion related complications, most importantly iron overload and related complications as well as alloimmunization against transfused red blood cell antigens [6–10]. The reported rate of alloimmunization

among transfused dependent patients with thalassemia varies between 4–50% and has a lower incidence in homologues populations. Some of these alloantibodies are important and even cause severe life-threatening transfusion related hemolytic reactions while others are clinically insignificant. Both of alloantibodies and autoantibodies may decrease survival of transfused pRBC and increase transfusion rate. Such patients may require immunosuppressive drugs, splenectomy as well as other alternative treatments. Therefore, alloimmunization and autoimmunization can significantly affect patients' quality of life and overall survival [11–13].

ALLOIMMUNIZATION IN THALASSEMIA MAJOR IN IRAN

A considerable number of studies were performed in patients with β -thalassemia major in different areas of Iran. The most common used method for detection of alloimmunization, was conventional tube technique (~80%), while gel method was used in minority (~20%) [5–8]. In the majority of studies, in addition to alloantibodies, autoantibody (8 out of 13 studies) (61.5%) also were detected [1, 3, 4, 12]. Among these studies, the rate of autoimmunization ranges from 1–~19% [4, 9]. The rate of alloimmunization varied between ~3–76%. The lower incidence of alloimmunization was reported in Tehran province, while the highest incidence was observed in Isfahan province [6, 9]. Among alloantibodies the majorities are against Rh and Kell blood group systems. The prevalence of alloantibody against Rh system ranged from 7.5–100% and this prevalence for Kell system varied from 14–60% [3]. Among these studies on Iranian patients, the rate of splenectomy was reported from ~8–100%. The rate of alloimmunization against these totally splenectomies patients was ~4% (Table 1).

In Rh blood group system, most of antibodies directed against E, C and c antigens respectively, while in Kell blood group system the majority were directed against K antigen (Table 2).

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Table 1: Prevalence of splenectomy and hemolytic reaction among Iranian patients with thalassemia major

Study	Splenectomy	Without splenectomy	Hemolytic reaction
1	28 (7.3%)	375 (92.7%)	Without hemolytic reaction
2	18 (25.7%)	52 (74.3%)	-
3	346 (41.4%)	489 (58.6%)	21 (2.5%)
4	222 (50.3%)	219 (49.6%)	7 (1.6%)
5	-	-	-
6	9 (17.3%)	43 (82.7%)	-
7	-	-	-
8	28 (21%)	105 (78.9%)	-
9	80 (100%) ¹	-	11 (13.75%)
10	7	-	-
11	10 (8.3%)	111 (91.7%)	-
12	17 (34.7%)	32 (65.3%)	-
13	203 (28.5%)	508 (71.5%)	-
Total	961	1934	39 (2.8%)

¹All of the patients had their spleen removed prior to the time of antibody formation.

Table 2: Prevalence of alloimmunization and autoimmunization among Iranian patients with β -thalassemia major

Study	Number of patients	Gender	Mean age	Province	Method	Allo-antibody	Majority of allo-antibodies	Number of antibody	Auto-antibody	Reference
1	385	Male: 221 Female: 164	13.8 y	Sistan and Baluchestan	Conventional	69 (17.9%)	Rh: 49.1% Kell: 14% Leu: 10.5%	Single	21 (5.5%)	1
2	70	Male: 31 Female: 39	16 y	Khuzestan	Conventional	6 (8.6%)	Rh: 50% Kell: 50%	Single	-	2
3	835 Adult (548) Pediatric (287)	Male: 416 Female: 419	Adult (24.5 y) Pediatric (10 y)	Tehran	Gel	100 (11.9%)	Rh: 45% Kell: 34% Colton: 2%	Single: 72% Double: 19% Triple: 3% UD: 6%	1 (1%)	3
4	441	Male: 234 Female: 207	22 y	Tehran + Qazvin	Gel	50 (11.3%)	Rh: 42% Kell: 28%	Single: 74% Double: 16% UD: 8%	1 (2%)	4
5	458	Male: 221 Female: 237	16.96y	Tehran	Gel	49 (11.8%)	Kell: 35% ³ Rh: 47%	Single: 71.5% Double: 14.3% UD: 14.2%	1 (2%)	5
6	52	Male: 36 Female: 16	18.2 y	Isfahan	Conventional	40 (76%)	Kell: 27.5% MNSs: 20% Rh: 7.5%	Single: 67.5% Multiple: 27.5% UD: 5%	-	6
7	218	Male: 100 Female: 118	22.5 y	Mazandaran	Conventional	88 (40.4%)	Rh: 75% Le: 64%	Single: 47% ⁴	-	7
8	133	Male: 66 Female: 67	17.5 y	Khuzestan	Conventional	25 (18.7%)	Rh: 55% Kell: 33%	Single: 72% Double: 20% Triple: 8%	17 (12.7%)	8
9	80	Male: 37 Female: 43	8.35 y	Tehran	Conventional	3 (3.7%)	Rh: 67% Kell: 33%	Single	15 (18.8%)	9

10	313	Male: 187 Female: 126	14.46 y	Northeast of Iran (Mashhad)	Conventional	9 (2.87%)	Rh: 100%	Single: 66.7% Double: 33.3%	--	10
11	121	Male: 55 Female: 66	13.0 y	Tehran	Conventional	9 (7.4%)	Rh: 22.2% Kell: 22.2%	Single: 100% UD: 5 (55.6%)	-	11
12	49	Male: 25 Female: 24	18.59 y	Zanjan	Conventional	8 (16.32%)	Rh: 40% Kell: 60%	Single: 75% Double: 25%	2.04 %	12
13	711	Male: 366 Female: 345	14.4 y	Shiraz	Conventional	38 (5.3%)	Rh: 36.3% Kell: 50%	Single: 92.1% Double: 7.9%	12 (1.7%)	13

Table 3: Prevalence of alloimmunization and autoimmunization among different countries

Ahmed et al.	2010	Egyptian	501	10.84 y ²	Gel	57 (11.3%)	Kell Rh	K: 35% C: 15.8% E: 29.8%	-	145 (28.9%)	14
Haslina et al.	2004	Malaysia	63	Adult (24.5 y) Pediatric (10.25 y)	Conventional	-	-	-	Single	1 (1.6%)	15
Pahuja et al.	2008 - 2009	Indian	211	Adult >5 y (80.6 y) Pediatric < 5 y (19.4 y)	Conventional	8 (3.79%)	Kell Rh	K: 25% E: 25%	Single: 75% Double: 25%	1 (.47%)	16
Al-Mousawi et al.	2014	Iraq	401	10.0 y	Conventional	18 (4.5%)	Rh Kell	E: 6 (30%) D: 4 (20%) K: 3 (15%) Cw: 3 (15%)	Single: 88.9% Double: 11.1%	-	17
S. Jansuwan et al.	2013	Northern Thailand	143	16.0 y	Gel and Conventional	24 (16.8 %)	Rh	E: 13 (54.2%) C: 4 (16.7%)	Single: 68% Double: 24% Triple: 8%	1 (0.7%)	18
Koçyiğit C, et al.	2011–2012	Turkey	139	Adult > 2 (37 y) Pediatric < 2 (102)	Gel and Conventional	9 (6.4%)	Kell Rh Kidd	K: 27% C: 27% D: 18% JKa: 18% E: 9%	Single: 77.8% Double: 22.2%	17 (12.2%)	19
Dogra, et al.	2009 –2010	Jammu region	70	9.27 y	Conventional	6 (7.5%)	Rh Kell	E: 50% K: 33.3 D: 16.7	Single	1 (1.42%)	20
AMEEN et al.	2002	Kuwaiti Arab and non Kuwaiti Arab	190	12.7 y	Conventional	142 (74.74%)	Kell Rh	K: 41 (72%) E: 26 (45.6%) D: 12 (21.1%) C: 9 (15.8%)	25 (43.8%)	21 (11%)	21
Hassan et al.	2003	Pakistan	75	6.5 y	Conventional	17 (22.7%)	Kell Rh	Kpa: 4 (23.5%) e: 3 (17.6%) E: 2 (11.8%) K: 2 (11.8%)	-	-	22
L.-Y. Wang et al.	2005	Taiwan	30	20 y	Conventional	11 (37%)	Rh	E: 7 (63.6) C: 2 (18.2%)	Single: 72.8% Double: 27.2%	-	23
N. Guirat-Dhouib et al.	2011	Tunisian	130	9.9 y	Conventional	10 (7.7%)	Rh	E: 3 (30%) C: 3 (30%)	Single: 80% Double: 20%	52 (40%)	24
Muhammad USMAN et al.	2011	Pakistan	800	11.5 y	Conventional	30 (3.75%)	Rh	D: 8 (26.6%) E: 7 (23.3%) c: 6 (20%) C: 5 (16.7%)	Single	-	25
Th. Spanosa et al.		Greece	1200	11.5 y	Conventional	220 (22.6%)	Rh Kell	K: 134 (28.5%) E: 66 (14%)	Single: 51.8% Double: 19.1% Triple: 13.6% More than three: 15.5	-	26

²calculated

COMPARISON BETWEEN ALLOIMMUNIZATION IN IRAN WITH OTHER COUNTRIES

Similar to Iran the most common antibodies against transfused red blood cells were anti-Rh and anti-Kell antibodies in other countries [14–22]. The rate of alloimmunization varies between these countries from ~4% in India and Pakistan to ~75% in Kuwait [16, 21, 22]. Similar to Iran, conventional tube method is the most commonly used method for antibody detection and identification in other countries [23–26]. Although as low as 0.7% of autoantibody was reported in other countries, most studies reported a significantly higher incidence of autoimmunization in other countries [18, 22–25]. In Kell blood group system, the most commonly alloantibodies directed against K antigen [14, 18–20]. In Rh blood group system, majority of antibody directed against D, E and C antigens (Table 3). With regards to these studies it seems that alloimmunization and even autoimmunization are a major concern in transfusion dependent thalassemia patients [5, 7, 22]. In Iranian patients with β -thalassemia major, transfusion related reaction was reported with a prevalence of about 15% in some studies [15, 20]. Sometime, in patients with alloimmunization is significant and can have life-threatening consequences. In emergency situations, appropriate blood selection is really difficult and required sophisticated laboratory investigations that only can be performed in specialized laboratories. In addition to this condition, clinically significant alloantibodies and autoantibodies can affect quality of life of these patients and affect overall survival of patients with β -thalassemia major. To prevent such conditions, its appropriate to use more suitable preventable strategies such as phenotyping of patients prior to beginning blood transfusion and used of relatively complete matched pRBC. Another way to prevent, is application of direct donation instead of random pRBC transfusion that increase the rate of alloimmunization and related consequences.

Keywords: Alloimmunization, Blood transfusion, Kell, Rh, β -thalassemia major

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Akbar Dorgalaleh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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