Iranian patients' attitudes to current and novel therapies: A patient directed survey

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Abstract

Thalassemia is one of the important challenges of the health system in Iran. Recently the medicinal drug of luspatercept and gene therapy have opened new horizons for thalassemia treatment. The present article aims to evaluate the attitude of thalassemics in Iran about the new treatments.

In this research, data collection through the virtual space has been practiced. The patients were required to declare their opinion on the aforementioned treatments. Finally, 128 male and 204 female plus 1 who did not specify their gender answered the questions. The results showed that despite patients' positive attitude towards new treatments, their treatment experiences as well as the expenses of the new treatment practices are cause of concern. Moreover, the social problems like unemployment among thalassemics place impact on their perspective about treatment changes.

Based on the findings of the present research, providing patients with more information about new treatment regimen and making their expenses compatible with the economic status of the developing countries would be effective in making the new treatments accessible to all eligible patients.

Introduction

Beta thalassaemia (BT) major is an inherited disease mostly prevalent in a region of the world known as the thalassemia belt.¹ One of the countries located in the belt is Iran with close to 4% of its population being thalassaemia gene carriers.² According to the latest reports, there

are 18,918 registered cases of haemoglobinopathy in Iran out of whom 15,954 are beta thalassaemia major.³ For this reason, prevention and management of thalassaemia are considered to be among the priorities of the health system of the country. The thalassaemia prevention programme started in 1995 country-wide⁴ and in the year 2015 it succeeded in decreasing the predicted thalassaemia births by 90%.³ Regarding thalassaemia management, Iran has a good experience in ensuring adequate and safe blood and providing patients with free country-level treatment and care. However, there are complaints about the locally produced drugs concerning their quality and also about the difficult access to imaging and bone marrow transplantation centres.³ Iranian success in thalassaemia prevention and treatment has led to the increase in the mean age of thalassemics and realized the hope of thalassemics living into their 4th decade of life.³ Thalassemics are participating in the arena of social life, and this strongly necessitates access to cure or to easier treatment regimens to facilitate better social integration.

In recent times, the news about the approval by regulatory agencies, *i.e.* European Medicines Agency (EMA) or Food and Drug Administration (FDA) in Western countries of innovative drugs for the treatment and cure of thalassaemia, including luspatercept⁵ and gene therapy,⁶ respectively, has led to increased expectations by both the health care professionals and in particular the patients. Given the importance of the patient's perspective in adopting new treatment strategies in thalassaemia, the present research aims to evaluate the viewpoints of patients with regards to these novel therapies.

Materials and Methods

In this research, a specific questionnaire was uploaded in Google form in which the individual's ID was requested to avoid the form being filled out multiple times by a single person. Access to the questionnaire was made possible from 18th May 2020 until May 22nd 2020 and the link to the questionnaire was available to patients across the country through WhatsApp, Telegram, Instagram, and Facebook. The first response was provided 10 minutes after the questionnaire was made accessible and the last one was obtained 3 hours and 27 minutes before the deadline. The responses were processed by SPSS and the results were analysed.

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Results

Out of 333 participants who answered the questionnaire, 128 (38.4%) were male and 204 (61.3%) female and 1 person had not indicated gender. The age related participation rate in the research is displayed in Table 1.

Out of 333 responses, 279 (83.8%) were provided by thalassaemia major patients, 46 (13.8%) by intermedia patients who were being transfused, and 8 (2.4%) by intermedia patients who were not being transfused (Figure 1).

Most of the respondents (79%) had a higher than high school diploma degree. The education status of participants is shown in Table 2.

With regards to professional status, 223 (67%) were unemployed, 43 (12.9%) part time employed, 44 (13.2%) full time employed, and 23 (6.9%) were self-employed.

The transfusion needs were appropriately addressed and reported by 285 (85.6%) responders while the rest (14.4%) responded and reported irregular transfusion intervals. The red cells provided to patients were processed as shown in Table 3.

Leukocyte-depleted blood was the red cell product most frequently provided to the patients.

Patients reported different experiences with regards to transfusion reactions; 218 reported experiencing alloimmunisation or other adverse transfusion-related reactions, grading them from severe to extremely severe reactions. The patient responses to this question are shown in Table 4.

From a total number of respondents, 149 (44.7%) reported that they believe that blood units are cross-matched for only a small number of antigen groups.

Concerning the day care transfusion facility, 91 (27.3%) of the patients reported that they are transfused at hospital-independent clinics with limited treatment facilities, 31 (9.3%) reported that they are transfused at treatment centres with expertise in blood disorders, 198 (59.5%) reported that they are treated in hospital haematology wards, and 12 (2.6%) reported being taken care of in hospital emergency departments (Table 5).

While 56 (16.8%) of the total patients are receiving hydroxycarbamide (hydroxyurea), the rest are on iron chelation treatment (single drug or combination) as shown in Table 6.

Quality of medications

146 (49.2%) of the responders reported that because of iron chelation-related side effects they had had to change chelating agent at least once in their life time. 197 patients (59.2%) mentioned difficulty in accessing the chelating agent of their choice, while 73 (21.9%) complained that the agent offered or made available to them, was not effective (based on serum ferritin levels and/or magnetic resonance imaging iron load measurements) or had side effects.

New treatment options

Patients were asked what kind of innovative treatment they would choose if they had the opportunity to do so. They were given four choices: gene therapy, agents reducing transfusion requirements, more effective iron chelation and 'others'. The responses are seen in Table 7.

Although 165 respondents (49.5%) had

a positive attitude towards gene therapy, a total of 232 patients raised concerns about gene therapy such as: i) having complications similar to bone marrow transplantation (related to myeloablation); ii) insufficient data on gene therapy complications; iii) high cost of gene therapy; and iv) other reasons mention (Table 8).

To the more specific question on the patients' perspectives with regards to the use of medical agents that could contribute to reduction of blood transfusion dependency, the patients responded as shown in Table 9.

260 (78.1%) of the responders expressed a positive attitude towards this approach. These agents include mainly hydroxycarbamide and luspatercept, authorised recently by EMA and FDA. However, the patients also raised concerns over the future of such treatments as shown at Table 9.

Similarly, 202 patients (60.7%) of the responders had a positive perspective on the use of potential new iron chelators albeit some concerns were also raised as shown in Table 10.

Figure 1. Types of thalassaemia among respondents. Transfusion Dependent Intermedia: Patients with thalassaemia intermedia who divert to transfusion dependency.

Figure 2. Blood shortage experience.

Table 1. Age.

Age	Frequency	Percentage	Valid percentage	Cumulative percentage
Valid				
Under 19	15	4.5	4.5	4.5
20-29	128	38.4	38.4	42.9
30-39	154	46.2	46.2	89.2
40-49	31	9.3	9.3	98.5
Above 50	5	1.5	1.5	100.0
Total	333	100.0	100.0	-

Patient experience with adequacy of blood supplies

The patient responses to blood adequacy, as this is defined in International Guidelines fall into two main categories as shown in Figure 2.

Almost half, *i.e.* 137 (41.4%) and nearly a third of the responding patients complained of blood inadequacy and of no observed shortages at all respectively dur-

ing the recent years.

Some key correlations related to the patients' attitude towards accepting/adopting innovative therapies.

Findings

- The findings demonstrate that there is a significant relationship between the personal experience of the patients with regards to facilitated procedures, safety

and adequacy of blood, appropriately processed and stored blood, transfusion-related adverse events and their attitude to adopting innovative treatments; correlation is significant at the 0.05 level (2-tailed).

- There was no significant relationship between the chelating agent used and the decision concerning the adoption of new therapies; correlation is not signifi-

Table 2. Education.

Education		Frequency	Percentage	Valid percentage	Cumulative percentage
Valid	No school education	8	2.4	2.4	2.4
	Under high school education	62	18.6	18.6	21.0
	High school diploma	120	36.0	36.0	57.1
	Associate degree	35	10.5	10.5	67.6
	Bachelor	78	23.4	23.4	91.0
	Master degree	24	7.2	7.2	98.2
	Above Master degree	6	1.8	1.8	100.0
	Total	333	100.0	100.0	-

Table 3. Type of red cells provided.

		Type of red cells (RBC) provided		Valid percentage	Cumulative percentage
		Frequency	Percentage		
Valid	• Packed RBCs	83	24.9	25.0	25.0
	• Washed RBCs	58	17.4	17.5	42.5
	• Leukocyte reduced RBCs using a bedside filter	128	38.4	38.6	81.0
	1 & 24	1.2	1.2	82.2	
	1 & 339	11.7	11.7	94.0	
	2 & 320	6.0	6.0	100.0	
	Total 332	99.7	100.0	-	
Missing	System	1	.3	-	-
Total		333	100.0	-	-

Table 4. Frequency and severity of transfusion reactions.

		Frequency and severity of transfusion reactions		Valid percentage	Cumulative percentage
		Frequency	Percentage		
Valid	• Very Intense	25	7.5	11.5	11.5
	• Intense	33	9.9	15.1	26.6
	• Moderate	74	22.2	33.9	60.6
	• Mild	30	9.0	13.8	74.3
	• Very mild	18	5.4	8.3	82.6
	1 & 25	1.5	2.3	84.9	
	1 & 31	0.3	0.5	85.3	
	1 & 41	0.3	0.5	85.8	
	2 & 38	2.4	3.7	89.4	
	2 & 51	0.3	0.5	89.9	
	3 & 411	3.3	5.0	95.0	
	4 & 52	0.6	0.9	95.9	
	1 & 2 & 3	3	0.9	1.4	97.2
	2 & 3 & 4	4	1.2	1.8	99.1
	1 & 2 & 3 & 4	1	0.3	0.5	99.5
	2 & 3 & 4 & 5	1	0.3	0.5	100.0
	Total 218	65.5	100.0	-	
Missing	System	115	34.5	-	-
Total		333	100.0	-	-

Table 5. Blood transfusion facilities.

		Blood transfusion facilities		Valid percentage	Cumulative percentage
		Frequency	Percentage		
1	Independent clinic with limited medical facilities	91	27.3	27.3	27.3
2	Comprehensive clinic for blood diseases	31	9.3	9.3	36.6
3	Hospital haematology wards	198	59.5	59.5	96.1
4	Hospital emergency department	12	3.6	3.6	99.7
	3 & 4	1	.3	0.3	100.0
	Total	333	100.0	100.0	-

Table 6. Types of iron chelation drugs.

		Blood transfusion facilities		Valid percentage	Cumulative percentage
		Frequency	Percentage		
Valid	• Deferoxamine injection	97	29.1	29.1	29.1
	• Oral deferasirox tablets	72	21.6	21.6	50.8
	• Oral deferiprone tablets	75	22.5	22.5	73.3
	1 & 2	24	7.2	7.2	80.5
	1 & 3	60	18.0	18.0	98.5
	2 & 3	3	0.9	0.9	99.4
	1 & 2 & 3	2	0.6	0.6	100.0
	Total	333	100.0	100.0	-

Table 7. Types of treatment.

		Types of treatment		Valid percentage	Cumulative percentage
		Frequency	Percentage		
Valid	• Permanent treatment such as gene therapy	83	24.9	24.9	24.9
	• An alternative that would reduce their blood transfusion frequency and duration	46	13.8	13.8	38.7
	• More effective iron chelation therapies with less side effects	44	13.2	13.2	52.0
	Other	17	5.1	5.1	57.1
	1 & 2	22	6.6	6.6	63.7
	1 & 3	21	6.3	6.3	70.0
	1 & 4	4	1.2	1.2	71.2
	2 & 3	42	12.6	12.6	83.8
	2 & 4	1	0.3	0.3	84.1
	1 & 2 & 3	40	12.0	12.0	96.1
	1 & 2 & 4	1	0.3	0.3	96.4
	2 & 3 & 4	3	0.9	0.9	97.3
	1 & 2 & 3 & 4	9	2.7	2.7	100.0
	Total	333	100.0	100.0	-

Table 8. Concerns expressed about gene therapy.

		Concerns expressed about gene therapy		Valid percentage	Cumulative percentage
		Frequency	Percentage		
Valid	• I am afraid of its side effects because it is similar to bone marrow transplantation	21	6.3	9.1	9.1
	• I am afraid of its side effects because I don't have sufficient information	47	14.1	20.3	29.3
	• I don't think I can afford it	65	19.5	28.0	57.3
	• Other reasons	14	4.2	6.0	63.4
	1 & 2	10	3.0	4.3	67.7
	1 & 3	10	3.0	4.3	72.0
	2 & 3	45	13.5	19.4	91.4
	3 & 4	2	0.6	0.9	92.2
	1 & 2 & 3	11	3.3	4.7	97.0
	2 & 3 & 4	4	1.2	1.7	98.7
	1 & 2 & 3 & 4	3	0.9	1.3	100.0
	Total	232	69.7	100.0	-
Missing	System	101	30.3	-	-
Total		333	100.0	-	-

cant higher than 0.05 level (2-tailed).

- The relationship between the development of thalassaemia complications *i.e.*, medical co-morbidities and the decision to adopt new treatments was found to be significant; correlation is significant at the 0.01 level (2-tailed).
- The acceptability of new treatments had no significant relationship with education level; correlation is not significant higher than 0.05 level (2-tailed).
- The experience of hydroxycarbamide use was shown to be significantly correlated with their preference to use inno-

vative medicines that contribute to decreasing transfusion dependence; the correlation is significant at the 0.05 level (2-tailed).

- There is a statistically significant difference for the future choice of treatment between male and female; the correlation is significant at 0.01 level (2-tailed).
- However, there is no significant correlation between the treatment centre used by the patients, their chelation regimen or their co-morbidities and their attitude towards using potential new chelators.

Discussion

Science has provided in very recent years important 'weapons' for the management and cure of thalassaemia and sickle cell disease (SCD): an innovative drug approved by EMA⁷ and FDA -luspatercept used in clinical trials- promises to reduce transfusion dependency to various levels on different patients based, mainly but not confined to the patients' genetic severity and Zynteglo⁸ (LentiGlobin BB305) which based on eligibility criteria and other parameters, promises the total cure (includ-

Table 9. Concerns raised about the use of alternative therapies.

Concerns raised about the use of alternative therapies				
		Frequency	Percentage	Valid percentage
Valid	• I do not have a good experience with hydroxycarbamide	10	3.0	6.5
	• I have no problems with blood transfusions	18	5.4	11.7
	• I am worried about the side effects of the drug	28	8.4	18.2
	• I don't think I can afford it	34	10.2	22.1
	• Other reasons	12	3.6	7.8
	1 & 2	1	0.3	0.6
	1 & 3	5	1.5	3.2
	1 & 4	4	1.2	2.6
	2 & 3	2	0.6	1.3
	2 & 4	2	0.6	1.3
	2 & 5	2	0.6	1.3
	3 & 4	18	5.4	11.7
	3 & 5	1	0.3	0.6
	1 & 3 & 4	5	1.5	3.2
	2 & 3 & 4	4	1.2	2.6
	3 & 4 & 5	5	1.5	3.2
	1 & 2 & 3 & 4	2	0.6	1.3
	1 & 2 & 3 & 4 & 5	1	0.3	0.6
	Total	154	46.2	100.0
Missing	System	179	53.8	-
Total		333	100.0	-

Table 10. Concerns raised about the use of new iron chelation treatment.

Concerns raised about the use of new iron chelation treatment				
		Frequency	Percentage	Valid percentage
Valid	• I am afraid of its side effects	33	9.9	18.3
	• I am afraid of its effectiveness	8	2.4	4.4
	• I have no problems with the current iron chelation treatment	47	14.1	26.1
	• I don't think I can afford it	34	10.2	18.9
	1 & 2	11	3.3	6.1
	1 & 3	7	2.1	3.9
	1 & 4	10	3.0	5.6
	2 & 3	1	0.3	0.6
	2 & 4	2	0.6	1.1
	3 & 4	8	2.4	4.4
	1 & 2 & 3	4	1.2	2.2
	1 & 2 & 4	7	2.1	3.9
	1 & 3 & 4	4	1.2	2.2
	1 & 2 & 3 & 4	4	1.2	2.2
	Total	180	54.1	100.0
Missing	System	153	45.9	-
Total		333	100.0	-

ing transfusion independency) of this disorder and soon for SCD as well.

In addition, a number of other drugs and genetic approaches for both management and cure of these disorders are well on the way with some of those in advanced clinical phases. Reliable knowledge and the patients' perspective on the use of these, is very important to be sought and obtained, both by Patient Organisations, health care professionals and very importantly by the industry and the decision makers, who (the latter) after all, will be requested to pay and make these innovative therapies accessible and available, as far as possible, to every eligible patient in need.

This survey reflects very efficiently that patients' perspective on the use of these therapies in Iran. Thalassaemia International Federation (TIF) has conducted a similar survey for patients across the world, the results of which will be shortly published.

Based on the findings of this research, the age distribution of the participants is compatible with that of the total Iranian population of thalassaemia patients.³ Thus, the survey responses can be considered to reflect the perspective of the total patient population in Iran. Nonetheless, the participation of women in the present study was significantly higher than the percentage of women in the female patient population in Iran.

The high unemployment rate in the survey participants may constitute an important reason for adopting a more negative attitude towards treatment changes that are related to high costs. The social problems faced by patients as well as their health status, are demonstrated in this survey to constitute important factors in their decision regarding their future choices for treatment.

Interestingly, about 50% of participants had a positive view of gene therapy albeit at the same time there is an expressed concern over the complexity of the gene therapy process, the complications that are related to the myeloablation part of the procedure⁹ and certainly its very high cost.

Regarding these concerns, it is clear that more patient oriented awareness and education are needed. The concern over the high cost of gene therapy requires further study to compare appropriately the cost of lifelong treatment *versus* cure through gene therapy. This exercise perhaps should be adopted in all countries so as to more accurately assess the national disease burden impacted by haemoglobin disorders in order for Governments to better acknowledge the need to adopt new, innovative curative approaches.

Similarly, the concern over medicines

decreasing transfusion dependence which also pertains to cost and complications reflects the lack of sufficient information dissemination regarding both the efficacy and the complications of these medicines. Moreover, it is appropriate that a more affordable, for each region, price of these medicines should be achieved particularly in view of the large patient population in the Middle East region including Iran. This is where a regional, and not a global, collaboration such as the initiative recently launched by TIF through the International Forum on *ACC*essibility, *E*ffectiveness and *S*ustainability of *T*herapies for Haemoglobin Disorders (TIF.ACCESS) Programme is important.¹⁰

The same concern exists for potential new chelators as far as patients' attitudes are concerned. The main patient concern in Iran is access to original brand medicines³ and this certainly affects their attitude in this regard. Transfusion dependence, age, gender, and occurrence of secondary complications in thalassaemia are considered to be the factors that have a significant effect on the decisions of the patients to *accept innovative therapies*, while other factors, such as the use of hydroxycarbamide, the type of treatment centre, and the recorded change in the type of chelators due to past complications, have had no significant impact on the patient decisions. The whole analysis shows that patients' attitudes towards the acceptability of future treatments in societies such as Iran is intertwined with complicated economic problems and does not follow a clear and integrated set of principles.

Conclusions

The findings of this research clearly shows that in order to have the true patient perspective on future choice of treatment, reliable and targeted education and comprehensive and reliable description of the pros and cons of the new treatments is needed. Further strength of advocacy skills of patients is needed in collaboration with health care professionals who will give appropriate and reliable information to patients and advise/guide them to more effectively make their choices. Moreover, the cost of new treatment choices particularly in developing economies should be based on their financial capacity so as to strengthen the access of patients to and the availability of these drugs to every patient in need or who chooses to take them.

It should be emphasized that in a society with high unemployment rate with consequent huge social challenges, the decision of patients to adopt a new treatment is great-

ly influenced and that informal decision by patients on new treatments requires continued awareness and education.

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