http:// ijp.mums.ac.ir
Original Article (Pages: 18413-18423)

Comparison of the Effects of Deferasirox (Nanojade®) and Deferoxamine (Desferal®) on Serum Ferritin Level Changes in Major Beta-Thalassemia Patients: A Randomized Clinical Trial

Saeedeh Khorashadi Zadeh [1], * Tayyebeh Chahkandi 2, Bita Bijari [3]

[1] Resident of Pediatrics, Department of Pediatrics, Faculty of Medicine. Birjand University of Medical Sciences (BUMS), Birjand, South Khorasan Province, Iran.

[2] Birjand Atherosclerosis and Coronary Artery Research Center, Associate Professor of Pediatric, Birjand University of Medical Sciences, Birjand, Iran.

[3] Professor of Social Medicine, Birjand University of Medical Sciences (BUMS), Birjand, Iran.

Abstract

Background: Different drugs with different mechanisms have been used to remove iron overload in thalassemia patients. This study aimed to compare the effects of Nanojade and Deferoxamine in reducing serum ferritin levels.

Methods: This randomized clinical trial was conducted on 41 major thalassemia patients. The selected patients were allocated to two groups by the permuted block randomization method. The first group was treated with Deferasirox (Nanojade) and the second group was treated with Deferoxamine (Desferal). All patients received the drugs at 14 mg/kg. Blood samples were collected at baseline, after 3 and 6 months after intervention. Chi-square test, Mann-Whitney U-test, and Friedman test were used for analytical statistics at the significance level of 0.05.

Results: 51.9% of patients in the Nanojade group and 40% in the Desferal group were females. Before the intervention, no difference was observed in terms of basic and demographic information. Before the intervention, as well as 3 months, and 6 months after the intervention, none of the blood parameters in the studied groups were significantly different ($p> 0.05$). The overall mean ferritin levels had a significant decrease, in both groups, 6 months after the intervention (PDeferasirox = 0.001 vs PDeferoxamine = 0.043); However, in the comparison between the two groups, no significant difference was observed between the levels of ferritin and creatinine at any of the time points ($p> 0.05$).

Conclusions: Deferasirox oral tablet (Nanojade®) is as effective as an injectable form (deferoxamine (Desferal®)) in reducing serum ferritin in patients with beta-thalassemia major without causing nephrotoxic effects. Therefore, it can be a suitable alternative to its injectable form.

Key Words: Beta-thalassemia, Deferoxamine, Deferasirox, Nanojade, Serum ferritin.

* Please cite this article as: Khorashadi Zadeh S, Chahkandi T, Bijari B. Comparison of the Effects of Deferasirox (Nanojade®) and Deferoxamine (Desferal®) on Serum Ferritin Level Changes in Major Beta-Thalassemia Patients: A Randomized Clinical Trial. Int J Pediatr 2023; 11 (12):18413-18423. DOI: **10.22038/ijp.2023.74803.5365**

****Corresponding Author:***

Tayyebeh Chahkandi, Birjand Atherosclerosis and Coronary Artery Research Center, Associate Professor of Pediatric, Birjand University of Medical Sciences, Birjand, Iran. Email: na_chahkandi@yahoo.com

Received date: Sep.04,2023; Accepted date: Dec.04,2023

1- INTRODUCTION

Thalassemia syndromes are the most common heterogeneous group of inherited single-gene blood disorders characterized by partial or complete deficiency of α-globin (alpha-thalassemia) or β-globin (beta-thalassemia) chain of hemoglobin (Hb) production, resulting in anemia ranging from severe to clinically asymptomatic individuals (1). The prevalence of this disorder in the world is estimated to be about 1.5% (80-90 million people) and the highest prevalence of this disorder is seen in the Mediterranean countries, Middle Eastern and Asian populations (2).

The survival of patients with beta-thalassemia major is dependent on the lifetime blood transfusion, which leads to iron overload and its toxicity effects on various organs. Complications of this disease in untreated cases include growth retardation, hepatosplenomegaly, hyperbilirubinemia, gallstones, endocrine disorders, cardiomyopathy, liver disorders, and ultimately premature death (3-5).

Iron overload is the main cause of pathogenesis in thalassemia patients. Diagnosis of iron overload is done by measuring the high level of serum ferritin or non-invasive imaging (6, 7). Ferritin levels above 300 ng/ml in men and more than 150-200 ng/ml in women during menstruation indicate iron overload (8). Suggested therapeutic strategies for this disease include using iron chelators, iron metabolism modifiers such as hepcidin, correcting the balance of globin chains by bone marrow and hematopoietic stem cell transplantation, gene therapy and cell therapy, and gamma-globin drug induction. The conventional treatment of this disorder is the use of iron chelators like Deferoxamine (DFO), Deferiprone (DFP) and Deferasirox (DFS) (3, 9).

Deferoxamine with the brand name Desferal is one of the most well-known iron chelators, used for more than 4 decades. Despite the occurrence of a small amount of cataracts, deafness, growth arrest and local skin reactions including urticaria, this drug is relatively non-toxic (10-12). However, despite the wide availability of DFO, some patients do not choose this drug due to its mentioned side effects (13). Based on the studies, the indication for starting treatment with subcutaneous DFO is after 10 to 20 blood transfusions or an increase in ferritin levels to more than 1,000 µg/l. Time-to-treatment initiation with chelators is 2 years after the start of blood transfusion and this process can take between 3 and 5 years (14).

Deferasirox has been evaluated in more than 45 clinical trials (Since 2003) and other studies have shown promising results (15, 16). It has been shown in many clinical studies that single daily doses of 10-40 mg/kg DFS cause a decrease in liver iron concentration, compared to DFO, and chronic blood transfusion in adults and children. DFS is generally well tolerated in adults, adolescents, and children 2 years of age and older (17, 18). DFS is available in some forms, including Exjade® (DFS - dispersible tablets, PO, once daily, completely dissolved in liquids), Jadenu® (DFS - granule formulation), and Nanojade® (a new film-coated tablet formulation of Deferasirox) in Iran pharmaceutical market (19, 20). In other studies, the method of combining two chelators such as Deferiprone with DFO or DFS was used and the results indicated an increase in life expectancy and a decrease in pathogenicity in people with iron overload (21, 22). Researchers are still searching for a drug that can be a suitable, less invasive, and cheaper alternative to DFO to reduce the economic burden and suffering imposed on the health system and society, along with increasing the life expectancy of affected patients.

Despite the mentioned information about the problems of thalassemia major patients

in removing iron overload, to the best of our knowledge, only a limited number of studies has been conducted in this regard, particularly in Iran. Considering the availability of the Iranian brand Deferasirox (Nanojade®) and its reasonable price, this study was designed to compare DFS (Nanojade®) and DFO (Desferal®) on serum ferritin level changes in beta-thalassemia major patients.

2- MATERIALS AND METHOD

2-1. Design and Participants

This randomized, parallel-group, un-blinded clinical trial was conducted on patients with beta-thalassemia major in Vali-e-Asr Hospital, the largest center for thalassemia patients in Birjand affiliated with Birjand University of Medical Sciences, Iran. Study samples were selected among thalassemia patients referred to Vali-e-Asr Hospital in Birjand, Birjand. The clinical trial protocol also follows the CONSORT checklist (**Fig. 1**).

2-1.1. Inclusion criteria and Exclusion criteria

All patients, over 2 years of age, with major beta-thalassemia were eligible for inclusion in the trial if they had these conditions: history of more than 10 blood transfusions or receiving more than 100 cc/kg of blood, serum ferritin above 1000 micrograms per liter, normal serum creatinine levels, absence of proteinuria, normal transaminase levels of Hepatic, not having hearing or vision problems, and willingness to participate in the study.

The exclusion criteria were as follows: Pregnancy and breastfeeding, any type of cardiac, hearing or vision problem, recurrent unexplained cytopenia in the patient, an increase of more than 30% of the baseline level in serum ferritin and its persistence for 3 months despite the appropriate dose of the drug, migration, or non-compliance with the protocol treatment.

2-1.2. Sample size calculation

According to the study of Rafati et al. (12) and based on the average ferritin at the end of the first two months in two groups, the sample size using the formula of comparing the averages in two independent groups considering type one error (α) of .05, effect size (d) of 0.9, and power of 80%. The calculation yielded a sample size of 21 for each group. Finally, 23 patients were determined for each group with consideration of a 10% attrition rate.

2-2. Procedure

2-2-1. Interventions

The first group was treated with Deferasirox (Nanojade®) + Deferiprone (L1) and the second group was treated with Deferoxamine (Desferal®) + Deferiprone (L1). All patients received drugs at 14 mg/kg, on an empty stomach and before breakfast with water or fruit juice.

2-2.2. Study implementation

After obtaining the necessary criteria to participate in the study, in case of informed consent regarding the treatment, the patients were allocated to 2 groups receiving Deferasirox and Deferoxamine. The available sampling method was used for sampling, and due to the special conditions of drug consumption, the allocation of patients to two groups was random. Patient information was collected by direct observation, clinical examinations by a specialist, and laboratory tests. A general questionnaire including demographic information and treatment, transfusion, and medication history was completed for each patient. Patients were treated with the mentioned drugs for 6 months. The required blood tests including CBC, ferritin and creatinine were checked and recorded in the

checklists of each patient before the intervention, as well as 3 months, and 6 months after the intervention. Average blood parameters in patients using Nanojade and Desferal have been compared before and after the start of the intervention.

Serum ferritin and creatinine levels were considered as the outcome of this study.

2-2. Randomization

The selected samples were randomly assigned to the intervention (Deferasirox) and control groups (Deferoxamine). To randomize patients into two equal groups, we used the permuted block randomization method; these blocks were designed randomly in Excel software, assigning (a) to the intervention group and (b) to the control group.

2-3. Data analysis

Data was analyzed using SPSS 21 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were presented as mean, standard deviation, frequency, and percentage. As a result of the non-normality of the data, as indicated by Kolmogorov-Smirnov test results, the chi-square test, Mann-Whitney U-test, and Friedman test were used for analytical statistics. The significance level was considered to be 0.05.

3- RESULT

In this study, 41 beta-thalassemia major patients were selected in two groups (Nanojade, n=21; Desferal, n=20) with an average age of 18.09±9.04 years (The minimum age was 3 years and the maximum was 35 years). Of the total participants, 21 (51.2%) were female, and most were in the age group of less than 15 years (43.9%). More details are presented in **Table 1**.

Based on the data included in **Table 2**, the averages of none of the blood parameters in the investigated groups significantly differ from each other. The results showed that three months after the start of the intervention, there was no significant difference between the averages of any of the blood parameters.

As shown in **Table 3**, the comparison of the mean ferritin level in the Nanojade group and Desferal group in any of the times before the intervention, and 3 months, and 6 months after the intervention, did not show any significant difference. It was observed that the mean ferritin level in the Nanojade group increased sharply three months after the intervention; and finally, in the sixth month, it decreased sharply and reached lower than the baseline level (P=0.001). The comparison of the mean ferritin level in the Desferal group showed significant changes (P=0.043), so that the mean ferritin level, unlike the Nanojade group, was continuously decreasing for consecutive months.

The mean creatinine levels in the Nanojade group and Desferal group were compared at different times before the intervention, as well as 3 months, and 6 months after the intervention. The results revealed no significant difference between the two groups in any of the mentioned times. In addition, the comparison of changes in the mean creatinine level in each group in different time points showed no significant difference between the changes in the mean creatinine level in any of the studied groups (More details are shown in **Table 4**).

4- DISCUSSION

The present clinical trial was designed to compare the effects of Nanojade (a new film-coated tablet formulation of Deferasirox) and Desferal (Deferoxamine) on serum ferritin level changes in patients with beta-thalassemia major, as the most important complication of blood transfusion, in South Khorasan province, Iran.

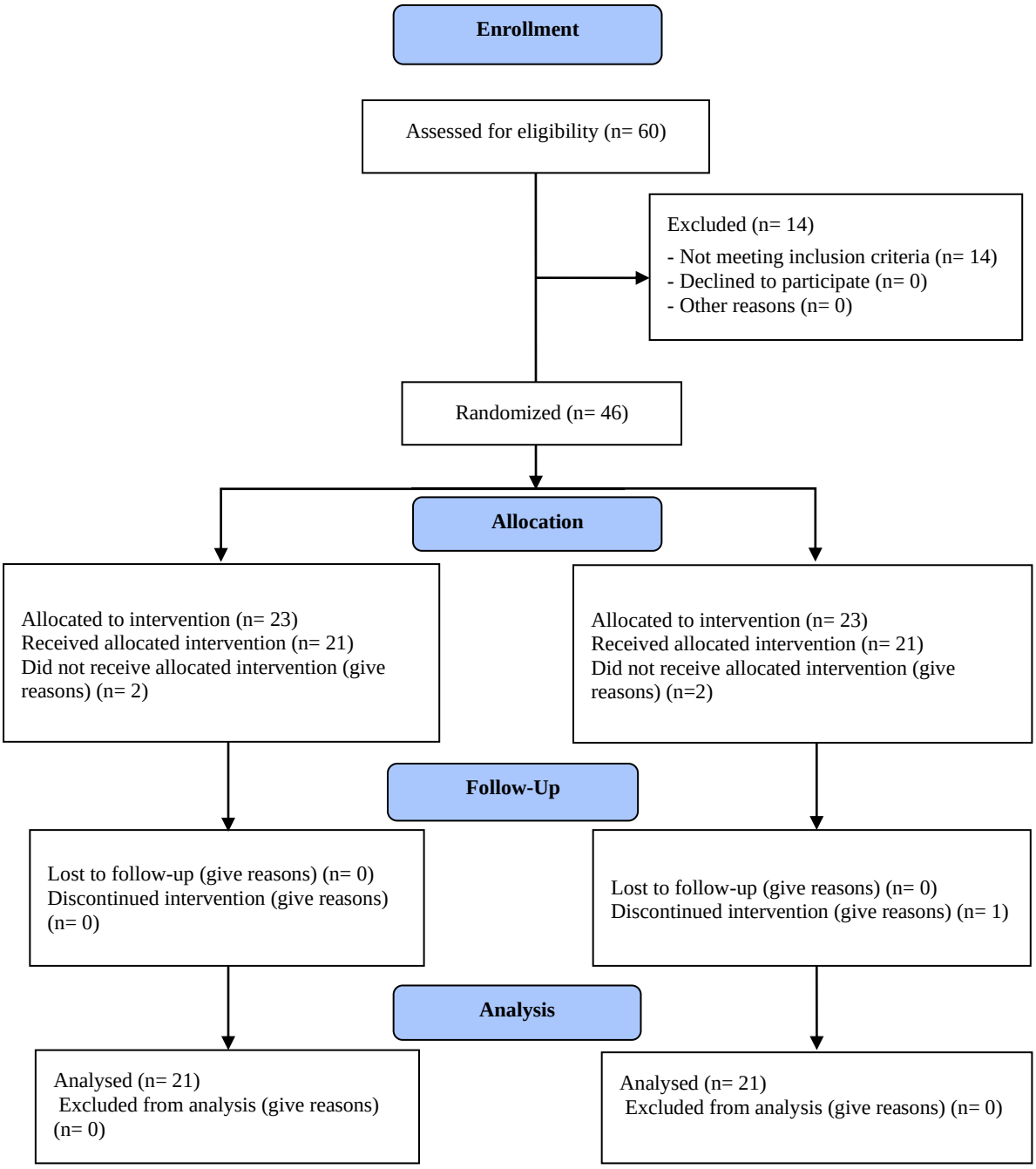

Fig. 1: The CONSORT 2010 Flow Diagram

Table-1: Demographic characteristics of patients with β-thalassemia major

Variable		Nanojade N (%)	Desferal N (%)	P value *
Sex	Male	8 (38.1)	12 (60)	0.16
	Female	13 (51.9)	8 (40)	
Age	<15	10 (47.6)	9 (42.8)	0.87
	15-25	7 (33.3)	8 (38.1)	
	>25	4 (19.1)	4 (19.1)	

* Chi-square test

Table-2: Comparison of blood parameters of patients with β-thalassemia major at baseline, after 3 months and 6 months after intervention

Parameters		Nanojade	Desferal	p-value*
		Mean ± SD	Mean ± SD	
RBC	Before	3.39 ± 0.41	3.34 ± 0.5	0.65
	After 3 m	3.34 ± 0.3	3.35 ± 0.3	0.94
	After 6 m	3.25 ± 0.27	3.28 ± 0.5	0.37
Hb	Before	9.63 ± 0.92	9.44 ± 1.5	0.56
	After 3 m	9.92 ± 0.87	9.81 ± 0.8	0.54
	After 6 m	9.78 ± 0.77	9.52 ± 1.3	0.85
HCT	Before	27.4 ± 5.72	27.1 ± 4.5	0.89
	After 3 m	31.4 ± 12.3	28.3 ± 2.5	0.36
	After 6 m	27.8 ± 2.32	26.7 ± 4.3	0.88
MCH	Before	27.8 ± 0.8	28.1 ± 1.1	0.5
	After 3 m	28.6 ± 0.7	28.5 ± 1.1	0.82
	After 6 m	29.6 ± 1.9	28.0 ± 1.3	0.05
MCHC	Before	33.7 ± 1.5	33.96 ± 1.1	0.62
	After 3 m	33.44 ± 0.82	34.25 ± 0.8	0.1
	After 6 m	34.75 ± 1.65	33.92 ± 1.3	0.35

* Mann-Whitney U-test

Table-3: Comparison of the mean ferritin level of patients with β-thalassemia major at baseline, after 3 months, and after 6 months of intervention

Ferritin	Baseline	After 3 months	After 6 months	P-Value*
	Mean ± SD	Mean ± SD	Mean ± SD	
Nanojade	3873.8 ± 2750.99	5979.47 ± 1286.09	2882.28 ± 2166.71	0.001
Desferal	4746.3 ± 3941.39	4010.4 ± 3264.87	3496.35 ± 2455.59	0.043
P-Value**	0.62	0.51	0.42	-

* Friedman test
** Mann Whitney U-Test

Table-4: Comparison of the mean creatinine level of patients with β-thalassemia major at baseline, after 3 months, and after 6 months of intervention

Creatinine	Baseline	After 3 months	After 6 months	P-Value*
	Mean ± SD	Mean ± SD	Mean ± SD	
Nanojade	0.69 ± 0.17	0.65± 0.10	0.63 ± 0.13	0.16
Desferal	0.73 ± 0.19	0.71 ± 0.15	0.68 ± 0.16	0.28
P-Value**	0.46	0.30	0.43	

* Friedman test
** Mann Whitney U-Test

The results showed that Deferasirox oral tablet (Nanojade®) is as effective as an injectable form (deferoxamine (Desferal®)) in reducing serum ferritin in patients with beta-thalassemia major without causing nephrotoxic effects.

The most important action in the treatment of patients with thalassemia major, after blood transfusion, is to reduce excess iron deposition and its consequences in the patient (14). In this study, we measured the serum ferritin level to measure iron overload. Although the measurement test of serum ferritin is non-specific and changes during various infections, tissue inflammations, liver diseases, hepatitis, and vitamin C deficiency, this test is the most common method of assessing iron overload and reflects tissue iron stores (23-25). If the serum ferritin level is more than 1000 µg/L after 10 to 20 blood transfusions, treatment with chelators is started (26). Common chelators include deferoxamine, deferiprone, and Deferasirox (27). The role of this progress of science in the fields of prevention, and permanent and temporary treatments cannot be ignored; as the life expectancy of these patients has increased from 17 years to more than 50 years during the last 5 decades (28).

In the comparison of serum ferritin levels between the two groups, no significant difference was observed between the mean ferritin levels of the patients at any of the time points at the beginning of the intervention, as well as 3 months and 6 months after the intervention.

Similar results were obtained in the study performed by Malik Hassan et al., about the effect of two drugs Deferoxamine and Deferasirox on serum ferritin level changes in beta-thalassemia patients in Cairo, Egypt. Although the brand of the studied drugs was not mentioned, after 12 months of taking the drugs, no significant difference was observed between the serum ferritin levels of the patients (29).

In comparing the mean ferritin level changes of patients in each group according to time, it was observed that in the Deferasirox group, the mean ferritin level of the patients increased sharply three months after the intervention, and in the 6th month after the intervention, it decreased significantly and reached lower than the baseline level before the intervention (P=0.001). In the study of Cappellini et al., patients were treated with different doses of Deferasirox (Exjade®). In low therapeutic doses (10 mg/kg/day), the mean ferritin level of the patients increased slightly in the first 18 months of treatment, but this value generally decreased in the next five years. In this study, the serum ferritin level of patients who were treated with higher doses of Deferasirox (20 and 30 mg/kg/day) the trend of changes was decreasing in the 5 year-period (30). In another study by Ahmed et al., patients with beta-thalassemia major were treated with Deferoxamine for 12 months and their serum ferritin levels were checked at three-month intervals. The results of that study showed that the mean serum ferritin of the patients decreased so that the ferritin level before the treatment with Deferoxamine was significantly higher than the ferritin level after 12 months, which was similar to the results of our study (31). So far, limited studies have been done regarding the new film-coated tablet formulation of Deferasirox (Nanojade®, Iranian brand) which was examined in this study. In a study on 80 beta-thalassemia major patients, Falahati et al. compared the mean ferritin of cases at 0, 3, 6, and 9 months in the groups receiving different brands of Deferasirox (Nanojade and Exjade) (20). Contrary to our findings, this study showed that the trend of ferritin changes was continuously decreasing in both groups, and no significant difference was observed between the ferritin levels of the two groups (20). A possible justification for

their findings about these continuous changes in serum ferritin levels could be the use of a higher dose in the research (20, 32).

In addition to iron, chelating drugs can bind to and remove some of the metals your body needs, such as calcium, copper, and zinc. This can lead to a deficiency of these important substances. Some people treated with chelation have low blood calcium levels and kidney damage (33, 34). Creatinine levels of patients, which is a way to diagnose kidney damage caused by increased iron overload in the body, were investigated in this study. The results of similar studies also did not show a significant difference between the average creatinine of the two groups (20). In the study by Unal et al., in the examination of the creatinine level of patients receiving Deferasirox, it was even observed that the trend of changes in the mean creatinine level of the patients was always downward (35).

4-1. Limitations of the study

The results of our study need to be confirmed by other studies with larger sample sizes, because one of the limitations of this study was the small sample size due to the limited number of patients with beta-thalassemia in Birjand city.

5- CONCLUSION

Based on the research findings, it is concluded that the general trend of decreasing ferritin levels in patients treated with Nanojade can indicate the proper efficiency of this drug in reducing serum ferritin. The comparison of ferritin between the two groups also showed no significant difference at 3 or 6 months. Therefore, it can be concluded that the oral form of Deferasirox (Nanojade), can be as effective as the injectable form of Deferoxamine (Desferal) in reducing serum ferritin. A comparison of creatinine levels in patients also showed no significant difference between the studied groups. Therefore, it can be concluded that none of the oral and injectable forms do not have nephrotoxic effects. Therefore, Nanojade as a more accessible brand for Iranian thalassemia patients, less invasive and cheaper than Deferoxamine, can be effective in reducing the economic burden and increasing the life expectancy of patients.

6- ETHICAL CONSIDERATION

The present study was registered in the ethics committee of Birjand University of Medical Sciences (Birjand, Iran) with the code IR.BUMS.REC.1401.263 and the clinical trial of Iran with the code IRCT20190817044550N4. After explaining the goals and procedures, written consent was obtained from the patients and it was explained that they could withdraw from the study if they wish.

7- REFERENCES

1. Mobasheri L, Chahkandi T, Talebpour A, Sarab GA. Red blood cell immunization among transfusion-dependent thalassemia major patients in Northeastern Iran. Asian Journal of Transfusion Science. 2023.

2. Galanello R, Origa R. Beta-thalassemia. Orphanet journal of rare diseases. 2010; 5:1-15.

3. de Dreuzy E, Bhukhai K, Leboulch P, Payen E. Current and future alternative therapies for beta-thalassemia major. Biomedical journal. 2016; 39(1):24-38.

4. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. Blood, the Journal of the American Society of Hematology. 2011; 118(13):3479-88.

5. Chahkandi T, Norouziasl S, Farzad M, Ghanad F. Endocrine disorders in beta thalassemia major patients. International Journal of Pediatrics. 2017; 5(8):5531-8.

6. Mishra AK, Tiwari A. Iron overload in beta thalassaemia major and intermediate patients. Maedica. 2013; 8(4):328.

7. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology 2014, the American Society of Hematology Education Program Book. 2017; 2017(1):265-71.

8. McDowell LA, Kudaravalli P, Sticco KL. Iron overload. 2018.

9. Motta I, Bou-Fakhredin R, Taher AT, Cappellini MD. Beta thalassemia: new therapeutic options beyond transfusion and iron chelation. Drugs. 2020; 80:1053-63.

10. Hajigholami A, Ansari H, Honarmand S. Comparing the efficacy of Dexeroyx (Osveral) and Deferoxamine (Desferal) in reducing serum ferritin level in patients with thalassemia major. Middle East J Fam Med. 2018; 7(10):218-22.

11. Mobarra N, Shanaki M, Ehteram H, Nasiri H, Sahmani M, Saeidi M, Goudarzi M, Pourkarim H, Azad M. A review on iron chelators in treatment of iron overload syndromes. International journal of hematology-oncology and stem cell research. 2016; 10(4):239.

12. Rafati M, Karami H, Lashtoo-Aghaee B, Lashtoo-Aghaee B, Dabirian M, Avan R. Two trade names of deferasirox (Osveral® and Exjade®) in reduction of iron overload parameters in major beta-thalassemia patients: A randomized open labeled clinical trial. Caspian Journal of Internal Medicine. 2022; 13(1):61.

13. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR, Network TCR. Complications of β-thalassemia major in North America. Blood. 2004; 104(1):34-9.

14. Bayanzay K, Alzoebie L. Reducing the iron burden and improving survival in transfusion-dependent thalassemia patients: current perspectives. Journal of blood medicine. 2016:159-69.

15. Fathi A, Vafaie M, Amani F, Mohebbi N. Evaluation of Osveral efficacy in reducing ferritin levels in patients with thalassemia major. International Journal of Basic & Clinical Pharmacology. 2017; 6(11):2556-60.

16. Saleem A, Waqar E, Shuja SH, Naeem U, Moeed A, Rais H, Ahmed J. No difference in myocardial iron concentration and serum ferritin with deferasirox and deferiprone in pediatric patients with hemoglobinopathies: A systematic review and meta-analysis. Transfusion Clinique et Biologique. 2022.

17. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, Aydinok Y, Kattamis A, Kilinc Y, Porter J, Capra M, Galanello R, Fattoum S, Drelichman G, Magnano C, Verissimo M, Athanassiou-Metaxa M, Giardina P, Kourakli-Symeonidis A, Janka-Schaub G, Coates T, Vermylen C, Olivieri N, Thuret I, Opitz H, Ressayre-Djaffer C, Marks P, Alberti D. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia. Blood. 2006; 107(9):3455-62.

18. Taher A, El-Beshlawy A, Elalfy MS, Al Zir K, Daar S, Habr D, Kriemler-Krahn U, Hmissi A, Al Jefri A. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with β-thalassaemia: the ESCALATOR study. European journal of haematology. 2009; 82(6):458-65.

19. Cheng WY, Said Q, Hao Y, Xiao Y, Vekeman F, Bobbili P, Sheng Duh M, Nandal S, Blinder M. Adherence to iron chelation therapy in patients who switched from deferasirox dispersible tablets to deferasirox film-coated tablets. Current Medical Research and Opinion. 2018; 34(11):1959-66.

20. Falahati V, Ghasemi A, Safari MR, Ghaffari K, Yousefichaijan P, Zamanian M. Renal function in patients with thalassemia major receiving Exjade®

dispersible tablets and a new film-coated tablet formulation of deferasirox (Nanojade®). Advanced Biomedical Research. 2022; 11(1):84.

21. Kolnagou A, Kontoghiorghe CN, Kontoghiorghes GJ. Transition of Thalassaemia and Friedreich ataxia from fatal to chronic diseases. World Journal of Methodology. 2014; 4(4):197.

22. Telfer PT, Warburton F, Christou S, Hadjigavriel M, Sitarou M, Kolnagou A, Angastiniotis M. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with deferoxamine and deferiprone. Haematologica. 2009; 94(12):1777.

23. Angulo IL, Covas DT, Carneiro AA, Baffa O, Elias Junior J, Vilela G. Determination of iron-overload in thalassemia by hepatic MRI and ferritin. Revista Brasileira de Hematologia e Hemoterapia. 2008; 30:449-52.

24. Elalfy MS, Saber MM, Adly AAM, Ismail EA, Tarif M, Ibrahim F, Elalfy OM. Role of vitamin C as an adjuvant therapy to different iron chelators in young β-thalassemia major patients: efficacy and safety in relation to tissue iron overload. European journal of haematology. 2016; 96(3):318-26.

25. Kwiatkowski JL. Clinical Challenges with Iron Chelation in Beta Thalassemia. Hematology/Oncology Clinics. 2023; 37(2):379-91.

26. Elalfy MS, Berdoukas V, Tricta F, Adly A, Hazza N, Awed H, et al. A Randomized Trial on the Safety and Efficacy of Early Start of Iron Chelation Therapy with Deferiprone in Newly Diagnosed Children with Transfusion Dependent Thalassemia. Blood. 2016; 128(22):1286.

27. Arya A, Jokar S, Etemadfar P, Malekzadeh JM, Jannesar R, Rohani M, Mohamadi T, Kharaman F, Yosefi6 M, Hatamipour S, Roozbehi A. Comparison of Deferoxamine, Deferiprone and Deferasirox Iron-Chelating Agents in Reducing Serum Ferritin Levels in Patients with Thalassemia Major %J Journal of Clinical Care and Skills. 2020; 1(4):189-93.

28. Farmakis D, Giakoumis A, Angastiniotis M, Eleftheriou A. The changing epidemiology of the aging thalassaemia populations: a position statement of the Thalassaemia International Federation. European journal of haematology. 2020; 105(1):16-23.

29. Hassan MAM, Tolba OA. Iron chelation monotherapy in transfusion-dependent beta-thalassemia major patients: a comparative study of deferasirox and deferoxamine. Electronic physician. 2016 ;8(5):2425.

30. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, Drelichman G, Economou M, Fattoum S, Kattamis A, Kilinc Y, Perrotta S, Piga A, Porter JB, Griffel L, Dong V, Clark J, Aydinok Y. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood, The Journal of the American Society of Hematology. 2011; 118(4):884-93.

31. Ahmed A, Kamran M, Mukhtar M, Ali M, Umair M. Comparison of deferasirox and desferrioxamine as iron chelators in multi-transfused patients of β-thalassemia major. Biological and clinical sciences research journal. 2023; 2023(1):270-.

32. Bird ST, Swain RS, Tian F, Okusanya OO, Waldron P, Khurana M, Durmowicz EL, Ma Y, Major JM, Gelperin K. Effects of deferasirox dose and decreasing serum ferritin concentrations on kidney function in pediatric patients: an analysis of clinical laboratory data from pooled clinical studies. The Lancet Child & Adolescent Health. 2019; 3(1):15-22.

33. Yang SK, Xiao L, Song PA, Xu XX, Liu FY, Sun L. Is lead chelation therapy effective for chronic kidney disease? A meta-analysis. Nephrology (Carlton, Vic). 2014; 19(1):56-9.

34. Jayalakshmi S, Venkatesan R, Deepa S, A. Vetcher A, Ansar S, Kim S-C. The effect of chelators on additives in the surface characterization and electrochemical properties of an eco-friendly electroless copper nano deposition. Scientific Reports. 2023; 13(1):11062.

35. Unal S, Hazirolan T, Eldem G, Gumruk F. The effects of deferasirox on renal, cardiac and hepatic iron load in patients with β-thalassemia major: preliminary results. Pediatric hematology and oncology. 2011; 28(3):217-21.