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Advances in Iron Chelation Therapy: Towards A New Oral Formulation

* Farid Ghazizadeh [1], Mehran Noroozi [2], Lachin Seifi [3]

[1] Assistant professor, Department of pediatrics, Faculty of medicine, Urmia University of Medical Sciences, urmia, Iran.

[2] Assistant professor, Department of pediatrics, Faculty of medicine, Urmia University of Medical Sciences, urmia, Iran.

3 Medical student, Urmia University of Medical Sciences, Urmia, Iran.

Abstract

Background: Patients with thalassemia major require regular monthly blood transfusion and excess iron from multiple blood transfusion deposits in different organs of the body, causing different organ damages. Cardiac iron overload is the main cause of death in patients with thalassemia major.

Method: The aim of this study was to determine the effectiveness of Deferasirox (Nanojade) produced in Iran for the first time as a medicine in reducing iron overload of chronic blood transfusion in patients with Beta-thalassemia major. This is a pre-post quasi-experimental study that was performed on patients with thalassemia major involved in lifelong regular monthly blood transfusions. In this study, based on the existing protocols, injectable and dissolving iron chelating regimes were changed to a new generation of deferasirox oral tablets. To determine the effect of Nanojade, the mean level of the last three serum ferritin levels, before changing chelation, was compared with the serum ferritin levels after starting Nanojade. In the course of treatment, the possible side effects of Nanojade in various organs were monitored regularly.

Results: The mean age of the patients was 16 years (ranging between 3 and 39 years). None of the patients had renal failure, elevated creatinine, or proteinuria with Nanojade. The most important side effect was elevated liver enzyme levels. The mean starting dose of Nanojade was 19.86± 5.78 mg/kg and the mean of the last dose was 23.41 ± 5.49 mg/kg. There was a statistically significant difference between the amount of ferritin at baseline with the serum ferritin of 6 and 18 months after chelation with Nanojade (P = 0.001).

Conclusion: chelation with Nano Jade had less renal and hepatic side effects; and all of the patients had good compliance and significant reduction in the serum ferritin level in comparison to the results of other studies regarding the similar foreign deferasirox products.

Key Words: Deferasirox oral tablets, Elevated creatinine, Thalassemia major, Iran, oral iron chelator, Iron overload, Nanojade, Proteinuria, Serum ferritin.

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Corresponding Author:

Farid Ghazizadeh, Assistant professor, Department of pediatrics, Faculty of medicine, Urmia University of Medical Sciences, urmia, Iran. Email: gazizadef@gmail.com

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1- INTRODUCTION

Thalassemia is an inherited anemia that occurs through mutated alleles of one or more globin genes (1). Thalassemia is one of the very common genetic disorders in Mediterranean countries, regions of North and West Africa, Middle East, the Indian subcontinent and Southeast Asia (2-4).

The prevalence of thalassemia in the north of Iran, around the Caspian Sea, is about 10%, in Isfahan 8%, in the southern regions of the country 8-10% and in other areas is between 4% - 8% (5). The leading cause of death in thalassemia major patients is iron overload in different organs of the body; especially the heart (6-8). Thalassemia major patients require regular blood transfusion that results in the deposition of excessive iron in different body organs. Iron overload leads to abnormalities in the endocrine system and damage to the heart and liver (9, 10). As a result, thalassemic patients need to receive iron chelating medications to reduce iron overload (12).

To date, there are 3 major classes of iron chelators: DFO (deferoxamine), Desferal®, a hexadentate by Novartis Pharma AG, Basel, Switzerland) in which 1 atom of iron is bound to 1 molecule of DFO, DFP (deferiprone), Ferriprox® a bidentate by Apotex Inc., Toronto, ON, Canada in which 1 atom of iron is bound to 3 molecules of DFP, and DFX (deferasirox), Exjade®, a tridentate by Novartis Pharma AG, Basel, Switzerland) in which 1 atom of iron is bound to 2 molecules of DFX (13).

Deferoxamine has been a lifesaving medication for thalassemia major patients in the last 50 years. Patients with thalassemia major have been dependent on slow subcutaneous infusions of deferoxamine for at least eight hours a day considering the short plasma half-life of the drug (12, 14). In spite of significant increase in life expectancy in patients with thalassemia major following the use of deferoxamine, the main cause of death is still heart disease due to iron deposition. Studies have indicated that subcutaneous infusion of deferoxamine might not be able to prevent excessive iron deposition in two-thirds of the patients with thalassemia major (15).

Prolonged subcutaneous infusion of deferoxamine with pump and also local side effects associated with its infusion cause major obstacles and impaired compliance of the patients, so the need for an oral iron chelator has been felt since a long time ago (15-17).

DFX (deferasirox), Exjade® is an oral iron chelator that is taken once a day. Exjade® was developed due to its long half-life and ease of use for patients. Exjade must be taken on an empty stomach with water, apple or orange juice, to limit variation in bioavailability (18). This chelator should be suspended in liquid and then consumed. This method leads to a long mixing process and is theoretically troublesome for patients, so many of the patients do not take it completely. Additionally, one-third of the patients consider Exjade® as an inedible medication (19). One-quarter of patients experience mild to moderate gastrointestinal (GI) symptoms, which may pose additional challenges, particularly in the younger and older age ranges (19).

The new generation of iron chelators, DFX formulation (Jadenu®), was developed in an attempt to overcome these tolerability issues. It is produced in tablet form by Novartis Company and is the only once-a-daily oral iron chelator that can be swallowed with a light meal, without the need to disperse into a suspension prior to consumption. It was approved by the FDA in March 2015 (20). When converting a patient from Exjade® to Jadenu®, the dosage should be decreased by 30 %, since

the new formulation is more bioavailable than the original Exjade® formulation (21).

Nanojade, produced in Iran by Nano Hayat Daru, is similar to Jadenu® in terms of formulation and has received all the required legal licenses from the ministry of health and FDA of Iran. It is distributed and available for thalassemia patients all over the country. The aim of the current study was to evaluate the efficacy of this Nanojade in reducing iron overload in patients with thalassemia major in Motahari center of Urmia University of Medical Sciences.

2- MATERIALS AND METHODS

This study was a quasi-experimental study performed on thalassemia major patients. Demographic information of the patients, history of previous iron chelation, baseline biochemistry laboratory tests including liver and kidney function tests, serology of viral hepatitis and serum ferritin levels, were extracted from medical records of the patients. Informed consent was obtained before the initiation of the study. Film coated Nanojade tablets manufactured by Nano Hayat Daroo Company which are available in 90, 180 and 360 mg formulations can be prescribed up to a maximum dose of 28 mg/kg daily. The starting dose of Nanojade was 14 mg/kg/day. In the course of chelation dose of the Nanojade was adjusted based on the ferritin level, iron input and blood transfusion. Follow-up of the patients during chelation with Nanojade was composed of monthly analysis of liver enzymes, serum creatinine and BUN, serum ferritin and urinary protein/creatinine levels. Mean of ferritin levels of the patients in the last three months before treatment with Nanojade was compared with serum ferritin levels after 3, 6 and 18 months of chelation with Nanojade. Based on the design of the study, liver enzymes were monitored at the beginning of the treatment and then monthly. In cases of liver enzymes more than 5 times the normal, chelation was discontinued. In patients whose liver enzymes did not decrease, after one month of discontinuing or increasing the resumption of the treatment, Nanojade was discontinued and chelation regimen was changed.

Serum creatinine levels were measured at the beginning of the study as baseline measurements. Dose of the Nanojade was halved and monitored weekly in patients whose serum creatinine levels increased to more than 33% of the baseline or more than twice the upper limit of the normal. In patients who did not achieve normal creatinine levels after 4 weeks of reducing the dose of Nanojade, chelation was stopped completely. Chelation was temporarily interrupted in cases who had a protein/creatinine ratio of greater than 0.6 in the spot urine test and if proteinuria was resolved, the chelation therapy was resumed. For patients with proteinuria lasting more than one month, the therapy was stopped forever. Patients with thalassemia major with a minimum age of two years and serum ferritin level of more than 1000 µg/l or more than 10 times blood transfusions or totally transfused blood volume more than 100 cc/kg were enrolled into the study. Patients with a gradual or persistent increase in serum creatinine level, cardiac, hearing or visual problems, those suffering from HBV, HCV or HIV infections, persistent hepatic transaminase elevation (5 times above normal), severe nausea and vomiting, (not controlled within 24 hours after diagnosis), persistent or progressive proteinuria, any medical or surgical intervention that can affect medication absorption, bioavailability, distribution, metabolism or excretion of the drug, patients with cytopenia (neutropenia < 1500/µl and thrombocytopenia < 150000/µl) and unexplained agranulocytosis (<500/µl), severe skin disorders (not controlled by corticosteroids after diagnosis) or allergic reaction to Nanojade were excluded from

the study. Pregnancy or breastfeeding, non-regular use of Nanojade by the patient and concomitant use of hydroxyurea, interferon or any other medication were also excluded from the study. Continuous drop of serum ferritin to below 500 µg/l was considered as temporary discontinuation of the treatment.

2-1. Data analysis

In this study, for quantitative variables central tendency and dispersion (mean and standard deviation) and for qualitative variables, frequency and frequency percentage were calculated. For comparison, statistical tests based on data distribution (normality) such as paired-t-test and chi-square or their nonparametric equivalents were used. Analyses were performed with SPSS version 21 software and the significance level was considered at 0.05 ($P \leq 0.05$).

3- RESULTS

22 transfusion-dependent Beta-thalassemia patients were subjected to receive Nanojade. Mean age of the patients was 16.31 ± 8.49 years (ranging from 3 to 39 years). 41% of the patients were male. There were 8 patients older than 18 years old. Before changing to Nano Jade, 13 patients were receiving deferoxamine and deferiprone, seven patients were on osveral (Osveral® is a brand name for Deferasirox manufactured by Osvah, the Iranian Pharmaceutical Company), and two patients were taking deferiprone and exjade, respectively.

Mean duration of the chelation with Nanojade was 16.81 months (ranging from 10 to 23 months). The mean level of serum aspartate transaminase (AST) and alanine transaminase (ALT) were 35.79 ± 15.52 U/L and 37.04 ± 33.36 U/L respectively. Mean serum level of total bilirubin and direct bilirubin were 2.71 ± 1.24 milligrams per deciliter and 0.57 ± 0.25 mg/dl, respectively. Based on the National Cancer Institute (NCI) common toxicity criteria for adverse events, in 8 cases there was grade 1 and 2 hepatotoxicity, but no more increase in liver enzyme levels was observed. Hepatotoxicity with elevated total bilirubin level (Grade 3) was reported in five cases. The mean creatinine level of the patients was 0.61 ± 0.15 mg / dl. None of the patients had elevated serum creatinine, proteinuria or renal failure during the treatment.

The mean starting dose of Nanojade was 19.86±5.78 mg/kg and the mean last dose was 23.41 ± 5.49 mg/kg at the end of the study. The maximum dose of the chelation, according to the deferasirox protocol was 28 mg/kg. All patients received the calculated dose regularly during the uninterrupted treatment period. Mean serum Ferritin levels at baseline and 3,6,18 months after treatment were, respectively, 3088.09±1644.13 ng/ml, 3133.06±2017.48 ng/dl, 2950.94±1988.85ng/dl, and finally 1950/05±1213/41 ng/dl **(Table 1)**.

Kolmogorov-Smirnov test results showed that ferritin levels at baseline, 3, 6 and 18 months after chelation with Nano Jade had a normal distribution ($P > 0.05$). The comparison of the mean ferritin levels at different time points was done by repeated measure tests. Mauchly test showed that the data has Sphericity (P-Muchy =0.092), so statistical Sphericity Assumed Test were used to examine the difference between ferritin levels at different times, indicating a statistically significant difference between ferritin levels at baseline with 3,6 and 18 months after treatment (P=0.001, **Table 2**).

Investigating the difference between two times with Bonferroni post hoc test (**Table 2**), a significant difference was revealed between the amount of ferritin level before the treatment and 6,18 months after the treatment (P=0.018).There was also a significant difference between ferritin levels 6 months after the treatment and 18 months after chelation therapy (P=0.019).

Table-1: Descriptive quantitative variables

Variable	Mean (SD)	min	max
Age (year)	16.31 (8.49)	3	39
Mean duration of treatment (month)	16.81 (3.73)	8	23
Initial dose (mg/kg)	19.86 (5.78)	10.74	36
Final dose (mg/kg)	23.41 (5.49)	10.74	37.89
Duration of receiving Nanojade			
10-12 months		5	
12-18 months		7	
>18 months		10	
Baseline Serum Ferritin (ng/dl)			
2000 >		5	
2000-3000		10	
3000 <		7	
Initial does (mg/kg)			
20 >		11	
20-25		9	
25 <		2	
Final does (mg/kg)			
20 >		8	
20-30		12	
30 <		2	

Table-2: Repeated Measurements in different times

Variable	P-value	F	p-value	χ^2	Mauchly's W
ferritin	0.001	6.49	0.092	9.48	0.618

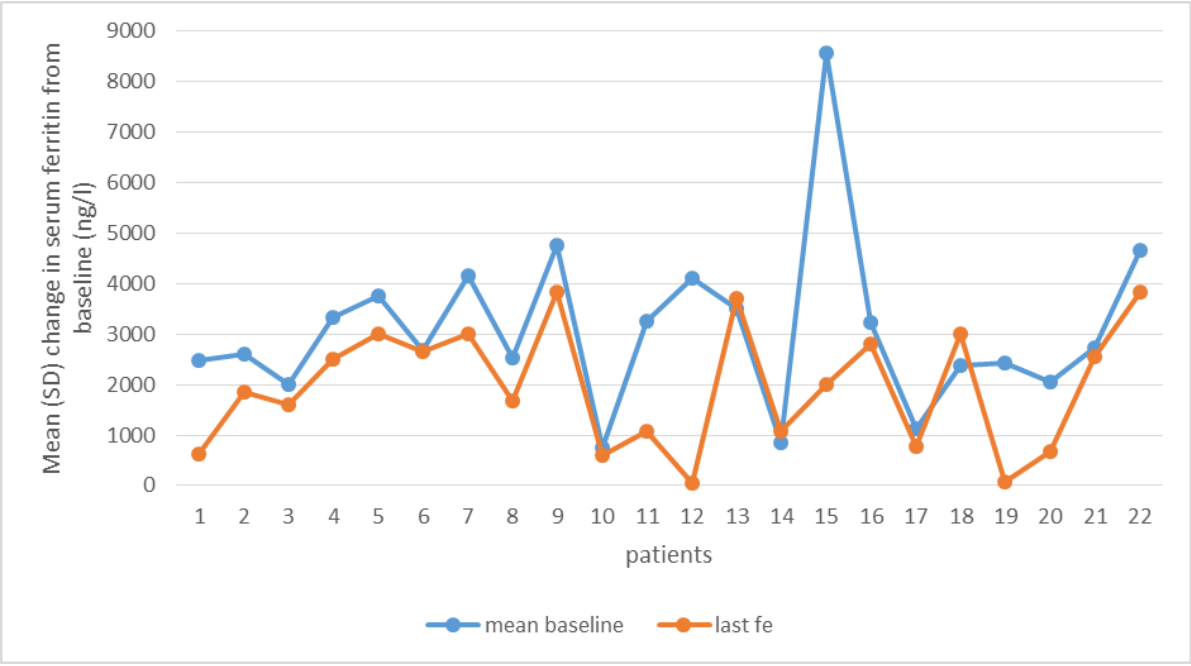

Fig. 1: change in serum ferritin from baseline by cases

4- DISCUSSION

This study has been designed to evaluate the efficacy and side effects of a new iron- chelation medication on the Nanojade®, the Iranian brand of deferasirox, due to its differences with previous chelation medications in formula, administration route, absorption, metabolism and the pharmacokinetic characteristics.

According to the guidelines for assessing iron burden and monitoring the efficacy of chelation therapy by serum ferritin and due to unavailability of LIC measurement in our center, in the present study serum ferritin level, instead of LIC measurement, was considered as an indicator of body iron burden (22).

All patients tolerated the initial dose and subsequent dosage increase without serious side effects, and none of the patients stopped chelation with Nanojade in the course of therapy. Compliance and treatment continuity in this study was better than those reported for Jadenu (non-Iranian made analogue of the Nanojade) in other studies (23). Contrary to the findings of the study by Tartaglione, testing Jadenu on 49 thalassemia patients, no gastrointestinal side effects such as nausea and vomiting were reported. The patients didn't need to be treated with proton pump inhibitors or anti-acids. In comparison to the previous generation of Nanojade, reducing gastrointestinal side effects have been now reduced, probably due the possibility of taking tablets with food along with its advantage of having no need for excipients (23).

In this study, more than 5 times increase in liver enzymes was considered as hepatotoxicity. Similar to Tartaglione's study, in none of the patients more than 5 times liver enzyme increase was reported during the treatment (24). In 8 cases hepatotoxicity grad 1 and 2 were observed but liver enzymes analysis showed no excessive increase in continuation of the same dose. In 5 patients hepatotoxicity grade 3 with elevated total bilirubin level was reported. Since liver enzymes, direct bilirubin level and liver ultrasound evaluation were normal in these 5 patients, treatment with Nanojade continued and finally no serious complications were observed.

In Tartaglione's study in more than 10% of patients, vomiting and proteinuria led to changes in doses and temporary discontinuation of the chelation; however, in our results none of the patients experienced renal failure, increase in creatinine and proteinuria (24). In ECLIPSE study, renal complications such as the common complication of deferasirox film-coated tablets (FCT) were reported, but in chelation with Nanojade no renal complications were observed (25). The discrepancy between results of this study and ESCALATOR study in the case of side effects may be due to the short duration of this study in comparison to the other studies. In the case of dermatologic and gastrointestinal side effects, it could be mild and not sensed by patients; and thus not reported by the family.

Considering the low initial dose of Nanojade with an average of 19.87mg/kg, no reduction in serum ferritin level is remarkable, and starting the chelation with higher doses would be effective in reducing ferritin. In all cases, the dose increase after the first 3 months was associated with a reduction in serum ferritin level.

5- CONCLUSION

Overall, the results of iron chelation with Nanojade® in iron chelating efficacy, safety and patient satisfaction were acceptable. But for more detailed results it is proposed that the study be reconducted for a more extended period of time with more patients. Also it is advisable to include other methods of iron overload

assessment such as liver tissue iron concentration and R2 MRI in the future studies.

6- ETHICAL CONSIDERATIONS

The research followed the tents of the Declaration of Helsinki. The institutional ethical committee at Urmia University of Medical Sciences approved all study protocols (IR.USB MSU.MSP.REC.13946.133900). This study was extracted from the M.D. thesis of Lachin Seifi at this university (98-0-32-1774).

7- CONFLICTS OF INTEREST

None.

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