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ORIGINAL ARTICLE

Efficacy of Deferasirox (Exjade®) versus Osveral® in Treatment of Iron Overload in Patients with Beta- thalassemia Major in Iran; A Non-randomized Controlled Trial

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ABSTRACT

Background: Iron chelators are an important part of management of patients with thalassemia. It is prudent to compare efficacy of different iron chelators in treatment of iron overload in these patients who receive regular blood transfusion. We aimed to compare the efficacy and safety of available oral iron chelator; Deferasirox (Exjade®) with Deferasirox (Osveral®) in reducing iron overload in patients with β-thalassemia major.

Methods: Children suffering from β-thalassemia major referring to Mofid Children Hospital were enrolled in this non-randomized clinical trial. The patients were divided into two groups receiving Deferasirox (Exjade®) versus Deferasirox (Osveral®) and their response to either treatment was assessed by measurement of serum ferritin levels and estimation of cardiac and liver iron by MRI T2* of heart and liver. Efficacy of either medication was compared before and after 12 months of treatment. Serum ferritin levels were measured every three months. Mean serum ferritin at baseline was compared with post-treatment values. MRI T2* of heart and liver was performed before and after treatment.

Results: Out of 69 patients with a mean age of 13.6±7.4 years, 42 (60.9%) were male. 30 patients were assigned to take Deferasirox (Exjade®) and 39 patients to take Deferasirox (Osveral®). The groups were not different regarding the age and the gender (P=0.18 and 0.621, respectively). There was no statistically significant difference in post-treatment serum ferritin level measurements between the two groups. In patients who received Osveral®, decrease in liver iron overload was significant (0.99 ms in Exjade® group vs 1.16 ms in Osveral® group, p=0.007). In the group of patients who received Exjade®, decrease in cardiac iron overload was significant (4.52 in Exjade group vs. 1.71 in Osveral group, P<0.001).

Conclusion: Deferasirox (Osveral®), the iron chelator manufactured in Iran, was as efficient as Deferasirox (Exjade®) in iron removal and could be a substitute for Deferasirox (Exjade®).

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Introduction

β-thalassemia is the most frequent hereditary anemia with a high prevalence in many countries.[1,2] It is considered the most common hereditary disease in Iran with approximately 26000 thalassemia major patients and three million carriers in the country.[3] This disease is associated with a high rate of morbidity and mortality; it induces anemia, splenomegaly, bone marrow expansion and bone deformities and requires life-long blood transfusion leading to iron accumulation and ultimately organ damage.[4,5]

Due to the fatal effect of iron accumulation in patients

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suffering from β-thalassemia major,[6] treatment with iron chelators is necessary for longer survival. Deferoxamine; a hexadentate, has been used since 1960s as the standard iron chelator and has been established to prolong survival of the patients with beta thalassemia major and decrease morbidity and mortality of the patients, but during the last decade its usage has been come to an obvious reduction in many countries as a result of mainly lack of compliance to it due to parenteral route of the medication, short half-life, organ toxicity and its adverse effects[7-9] which accounts for more than 67% of the mortality of β-thalassemia patients.[10] Thus, researchers have been looking for a more proper drug with higher efficacy and compliance and lower complications. Deferasirox (Exjade®, ICL670); a tridentate can be orally absorbed and has a half-life of 11-19 hours which can be prescribed once daily.[11,12]

Osveral® is a brand name for Deferasirox manufactured by Osvah, an Iranian Pharmaceutical Company. Osveral® received its marketing authorization through National Food and Drug Department of Iran Ministry of Health and is among the drugs reimbursed by national health insurance scheme. We aimed to compare the efficacy and safety of Deferasirox (Exjade®) versus Osveral® in transfusion dependent thalassemia major patients with evidence of transfusion induced iron overload.

Patients and Methods

We conducted a non-randomized clinical trial in which 69 patients with β-thalassemia major referring to Mofid Children's Hospital were enrolled. Eligible subjects received detailed explanations about the study and informed consent was obtained. For patients younger than 18 years of age, the informed consent was obtained from their parents or guardians. This study was conducted in concordance with the principles of the Declaration of Helsinki. Approval for the conduct of this study was obtained from the Research Ethics Committee and Institutional Review Board of Shahid Beheshti University of Medical Sciences. This trial has also been registered in International Clinical Trials Registry Platform (registration number: IRCT2015102524679N2). We included thalassemic patients older than 2 years who had received more than 10 times blood transfusion and had not compliance for taking Deferoxamine. The patients should have normal serum levels of creatinine, serum levels of liver transaminases less than 5 times the normal value, normal complete blood count and serum ferritin levels higher than 1000 ng/ml. Exclusion criteria comprised of patients with heart failure, positive for hepatitis B, C and HIV, presence of proteinuria, severe nausea/vomiting, skin rash or any other disease in which performing MRI is contraindicated. It was a non-randomized control since the decision on taking Exjade versus Osveral was mainly based on affordability of the medication by parents.

Primary outcome parameters were determining iron overload status of the patients; at baseline and 12 months after treatment with iron chelators, which was achieved by measuring the mean serum ferritin level and assessment of cardiac and liver iron content by MRI T2*. Secondary outcome parameters included determination of the mean dose of the prescribed Deferasirox (Exjade®) and Osveral® and their adverse effects.

Participants received either Deferasirox (Exjade®) (Novartis CO., Stein, Switzerland) or Osveral® (Osvah Co., Tehran, Iran), whichever they could afford. The starting dose for either drug was 20 mg/kg/day which was reduced or increased by 5-10 mg/kg/day according to changes in serum ferritin levels; so that ranged between 10-40 mg/kg/day. Serum levels of ferritin were measured in three-month intervals. Mean serum ferritin levels, measured three times during the last 6 months before the start of the treatment was considered as the baseline value and was compared with post-treatment values checked every three months.

MRI was performed before and one year after starting the trial. In liver, relaxation times higher than 6.3 ms was considered as normal, 2.8-6.3 ms as mild, 1.4-2.8 ms as moderate and less than 1.4 ms as severe iron overload. In heart, MRI relaxation time higher than 20 ms was considered as normal, 15-20 ms as mild, 10-15 ms as moderate and less than 10 ms as severe iron overload. According to a previous study,[13] MRI T2* is the most sensitive method for measuring cardiac and liver iron content. The dose of the drugs were tailored according to serum ferritin level for each patient. The probable adverse effects of Exjade® or Osveral® were registered in the patient's data sheet through history taking and physical examination in each visit. Nephrotoxicity was diagnosed if rise in creatinine on two consecutive visits was observed. Also if aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels were increased to ten times the normal, hepatotoxicity was suggested. The drugs were discontinued if nephrotoxicity or hepatotoxicity was occurred.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, IL, USA). To assess distribution of the continuous variables, Kolmogorov-Smirnov test was performed. Descriptive statistics were given by means and 95% confidence interval for normally distributed data. Categorical data were listeded by absolute and relative frequencies. In analytical statistics, Nominal or ordinal variables were compared between groups by chi-square test and Fisher's exact test, depending on the expected cell counts of the corresponding crosstabs. In addition, unpaired Student *t*-test was used when the variables fulfilled the presumption of normal distribution, whereas the Mann-Whitney *U* test was used when the variables were not normally distributed. Paired t-test was applied to compare the values before and after the study. The results of the two-sided tests were considered significant if p-value was less than 0.05.

Results

69 patients affected by beta thalassemia major were enrolled into the study. Thirty patient were assigned to take Exjade® and 39 patients to take Osveral®. Mean age of the patients was 13.63 years (95% CI, 11.59-15.43 years). There was no difference between the two groups in terms of age. Forty two patients were male and twenty

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seven were female (P=0.53).

Mean serum ferritin levels are shown in table 1. They showed no statistically significant difference between the two groups at the beginning, duration of the study (every three months) and end of the study. The mean dose of Exjade® and Osveral® during the study was 29.69 mg/kg/day and 25.87 mg/kg/d, respectively.

Changes in liver iron overload assessed by MRI T2* was not significant in Exjade® group during the study, but in Osveral® group the improvement (decrease in liver iron overload) was significant (0.99 ms in Exjade® group vs 1.16 ms in Osveral® group, P=0.007). In the group of patients who received Osveral®, the change in cardiac MRI T2* was not significant; however, in Exjade® group the improvement (decrease in cardiac iron overload) was significant (4.52 in Exjade group vs. 1.71 in Osveral group, P<0.001) (table 2).

Skin rash was seen in 7 (17.9%) patients in Exjade® group and 5 (16.7%) in Osveral® group (p=0.88). Increasing liver transaminase levels were seen in 5 (12.8%) in Exjade® group and 5 (16.7%) in Osveral® group (p=0.653). The rising of serum creatinine was significantly lower in Osveral® group in compared with Exjade® group (53.8% in Exjade® vs 26.7% in Osveral® group).

Increased protein to creatinine ratio (>0.6 mg/mg) was seen in two participants. One in Exjade® and one in Osveral® group.

Discussion

Transfusional iron-overload is a challenging issue in treatment of thalassemia patients who receive regular blood transfusions. It should be managed using chelating agents such as Deferroxamine (Desferal®), Deferiprone (Ferroprox®) and Deferasirox (Exjade®).[14] Deferasirox which is an oral iron chelator has been shown to have similar efficacy and safety compared with Deferroxamine in patients with β-thalassemia in previous studies.[15-17]

Cappellini et. al in a longitudinal study indicated the efficacy and safety of Exjade® after 5 years follow-up.[18] Alavi et. al have proven the efficacy of Deferasirox (Exjade®), particularly in mild to moderate iron overload with 67% success rate in Iranian children at optimal doses of 30-40 mg/kg/day.[19] Cassinerio and co-workers evaluated the efficacy of Exjade® in prevention and removing cardiac and liver iron and cardiac volume changes on 23 thalassemia patients using T2* cardiovascular magnetic resonance (CMR). They found that after 5 years of treatment, Exjade® significantly reduced myocardial and liver iron overload and prevented further iron deposition.[11]

Molavi and co-workers conducted a clinical trial on 80 patients with thalassemia receiving Osveral®. They determined the efficacy of this agent by measurement of serum ferritin levels during a one-year period of treatment. In this study, decreasing trends in serum ferritin levels was observed; however, small increases were noted in the first three to four months of the treatment.[20] In a multicenter study on 407 patients with talassemia, the researchers evaluated the efficacy and safety of Osveral® in Iranian patients. The results showed a promising profile of safety and efficacy of Osveral®.[21]

The results of the current study showed the efficacy of Osveral®, assessed by MRI T2 * of heart and liver was similar to that of Exjade®. Increased serum creatinine was the most serious complication in this study. Other complications such as skin rash, increased liver transaminase levels and high protein/creatinine ratio were not different between the two groups. Similarly, Eshghi and colleagues reported increase in serum creatinine as the most common complication of Osveral (24%). Cappellini and colleagues have also reported increase in serum creatinine level as the most common adverse effect of Exjade.[20] In current study this complication was statistically more observed in the exjade group (P=0.029).

Eshghi and co-workers reported elevated liver transaminase levels in 6% of participants who received Osveral;[21] whereas, it was present in 14.5% of the participants in our study. Although their study included a high number of cases from nine centers, their study did not have any control group to compare the efficacy and

Table 1: Mean and standard deviation of serum ferritin levels in two groups of thalassmic patients receiving Exjade vs Osveral

	Exjade®	Osveral®	P value
Baseline ferritin, ng/ml	1796±1040	1900±1007	0.68
Ferritin level in the first three months after intervention	1948±1006	2085±986	0.58
Ferritin level in the second three months after intervention	2020±1163	2097±922	0.77
Ferritin level in the third three months after intervention	2419±1192	2045±907	0.19
Ferritin level, twelve months after intervention	2072±680	1978±1058	0.81

Table 2: Liver and cardiac MRI T2* before and after intervention

	Mean (95% CI), ms	P value
Liver MRI-T2 * before intervention in Exjade group	4.72 (3.76-5.38)	0.377
Liver MRI T2 * before intervention in Osveral group	4.14 (3.54-5.30)	
Liver MRI T2 * after intervention in Exjade group	6.29 (4.5-7.28)	0.376
Liver MRI T2 after intervention in Osveral group	5.31 (4.31-6.31)	
Heart MRI T2 before intervention in Exjade group	26.20 (23.56-28.7)	0.014
Heart MRI T2 before intervention in Osveral group	21.41 (18.73-23.87)	
Heart MRI T2 after intervention in Exjade group	30.42 (28.02-32.92)	<0.001
HeartMRI T2 after intervention in Osveral group	23.13 (20.52-25.83)	

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also the adverse effects.

Galanello et. al have also evaluated deferasirox safety in a phase II clinical trial in 2006 in 39 pediatric patients and have reported good tolerance, no toxicity, and no cases of mortality, but they reported four cases of severe adverse effect that included mild nausea and skin rash.[22]

The current study indicated that dose of treatment was not different between two groups receiving exjade *vs* osveral. The ESCALATOR study and other studies[23,24] have confirmed that the efficacy of deferasirox is dose-dependent and that dose adjustments should be closely observed in patients suffering from β-thalassemia for the utmost efficacy of the drug.

The strengths of the current study includes comparing the efficacy and safety of two drugs for iron clearance of the liver and heart by a standard method before and after treatment in a center specialized for thalassemia in Iran.

In conclusion, osveral, manufactured in Iran, is as efficient as exjade, manufactured in Switzerland for iron chelation and can be a good substitute for it in Iran, where the main drug is more expensive. We conclude that use of Osveral represents a cost-effective option for treatment of iron overload in Iranian patients with β-thalassemia and could be used as an alternative to Exjade in patients with low income.

Conflict of Interest: None declared.

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