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Research Article

Effect of deferasirox therapy on serum ferritin level and its side effect in Iraqi thalassemia patients

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ABSTRACT

Deferasirox is an iron chelating drug of oral intake. It is main use is to decrease iron overload in patients who are receiving blood transfusions for a long time in conditions such as beta-thalassemia and other chronic anemias. This study was aimed to determine the benefit of the oral chelating agent (Deferasirox) and it is a side effect in thalassemia patients. Fifty patients with a provisional diagnosis of thalassemia major and transfusional iron in Aldiwaniya province /Iraq in the period (August 2015 –April 2017). Most of the patients were managed according to the own protocol with the target hemoglobin levels around 9.5-10.5 mg/dl before blood transfusion. Serum ferritin estimation was advised after at least ten packed red cell transfusions. The oral chelating was started to inform of deferasirox oral tablet in doses of 10 to 20 mg per kg per day if ferritin levels in serum reached > 1000 ng per ml and 20-40mg/kg if serum ferritin more than 1500ng/ml. Those patients were switched to deferasirox, as an oral chelating agent without used any other chelator. The patients were classified based on the age groups (less than and above 10 years) and according to gender. The average level of ferritin in the serum of these group at the initiation of the study was 2678.83 ng/ml before treatment and 2255.43ng/ml after deferasirox commenced. The study group recorded a good compliance in 70% and poor in 30%. Patients treated with deferasirox showed some gastrointestinal symptoms like abdominal cramps, vomiting, and diarrhea in 12% of cases and skin rash in 2% and increase in a liver enzyme in 4%. Deferasirox is well affordable with long-term treatment and the adverse effects are minimal with this medication; therefore optimum treatment is needed to produce the good clinical result and decrease or no adverse effects in a good acceptable dose; however the occurrence of therapy-related adverse effect decreases with time and the common therapeutic complications reported are related to gastrointestinal symptoms and skin rash in some patients and increase in liver enzyme .The availability of this therapy (oral iron chelators), like deferasirox, may take part to produce good satisfaction, especially among young child and school-age patients in which the compliance is a very big problem.

Keywords: Deferasirox; Ferritin; Oral Chelating Agent

INTRODUCTION

Deferasirox (marketed as Exjade) is a chelating agent against iron. It is mainly used is to decrease iron overload in patients who are receiving blood transfusions for a long time in conditions like beta-thalassemia and other chronic diseases require frequent blood transfusions (Choudhry et al, 2007, Yang et al, 2007). It is the first oral therapy authorized in the USA for chronic transfusions diseases. The approval time by (Food & Drug Administration) in November 2005(FDA). According to FDA (May 2007); kidney failure and pancytopenia and other complications have been reported in patients receiving deferasirox oral suspension tablets. It is approved in the European Union by the European Medicines Agency for patients six years age and more for chronic iron overload from repeated blood transfusions.

The phlebotomy method cannot be used to scavenge iron in patients with frequent blood transfusions (like thalassemia different type of thalassemia's, aplastic anemia sickle cell anemia and myelodysplasia) with iron overload or those patients rarely present with hemochromatosis and hemodynamically unstable (like severe heart involvement) (Fabio et al, 2007). A tight regulation of iron balance is essential to avoid both iron deficiency and overload. The iron metabolism regulation depends on a number of specific proteins as well as the balance between iron loss, iron in tissue and circulations, and iron absorptions (Hertz et al, 2010). The main treatment for β-thalassemia primarily involves the chelation of iron. Every packed of transfused red blood cells contains nearly 2 hundred milligram iron. Moreover, defective erythropoiesis and anemia control the hepcidin formation (Ganz et al 2010, Liu et al, 2016).

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The main aim of iron chelation is to avoid the adverse event of iron accumulation in essential organs like heart and liver. Iron Chelation treatment improves myocardial T2* and ventricular function (Maggio et al, 2012, Cassinerio et al, 2012). iron-chelating therapy should have a certain option added to its capability for iron binding, like biological availability orally and single dose per day intake. the Deferasirox return to a certain type chelators belongs to tridentate, N-substituted bis-hydroxyphenyltriazoles which responsible for the program of discovery. many preclinical studies demonstrate the efficacy and safety of drug (Hershko et al,2001) phase one and phase two studies in adult patients (Brown et al, 2003, Piga et al,2003) and children with thalassemia (Piga et al, 2004). Its half-life of (eight sixteen) hours, single daily regimen allows the agent to clean iron at all time that no bound to transferrin (Daar et al, 2005). The combinations of other chelating agents with deferasirox have also been evaluated. The combination of deferasirox and deferiprone produced a higher reduction in serum ferritin, greater improvement in heart T2* and improve quality of life, and good compliance compared with the combination of deferiprone and deferoxamine. So, this study was designed to determine the benefit of the oral chelating agent (Deferasirox) and it is a side effect in thalassemia patients.

PATIENTS AND METHODS

Fifty patients with a provisional diagnosis of thalassemia major and transfusional iron overload diagnosed by detection of s. ferritin > 1 thousand ng/ml were involved in the study, were studied at hematology and thalassemia teaching center in Al-Diwaniya province, Iraq in the period (August 2015 –April 2017). Most of the thalassemic child were treated according to the own regimen with target hemoglobin value between 9.5-10.5 mg/dl before blood transfusion. Serum ferritin estimation was advised after at least ten packed red cell transfusions. The oral chelating was started to inform of deferasirox oral tablet if the level of ferritin in serum > 1000 ng/ml. Those patients were giving the only deferasirox, as an oral chelating agent without using any other chelator. We prefer to classify those patients based on the age groups (less than and above 10 years' age) and according to gender.

The patients of ferritin value in serum range from one thousand to one thousand and a half ng/ml or those require 10ml/kg blood transfusion per month, a dose of 10-20 mg per kg per day of deferasirox of started; and those with s ferritin value > 1500 ng per ml or requiring 20 ml/kg/month of packed red cells (twice blood transfusion per month) dose may reach to 40 mg/kg per day of deferasirox. The adjustment of the dose based on the level of ferritin in serum and if there were side effects appear and according to the general conditions of the patients. Full general examination and a baseline investigations include serum creatinine, blood urea, and the liver enzyme was measured along with at least two serum ferritin levels before treatment and these investigations and examinations were repeated at monthly interval. The levels ferritin in serum measure every three months.

The less than two years old child and the patients with other chronic illness or that used other chelators were excluded from this study. In order to improve the compliance, parents were asked for recording the drugs intake seen with every visit. The data was analyzed use SSPS program and the Chi-Square statistic is used for testing relationships between variables.

Statistical Analysis

Data were collected and transferred to SPSS (version 23) spreadsheet and analyzed and were presented as a mean and standard deviation. Independent samples t-test was used to compare mean age and serum ferritin between study and control groups.

RESULT

Total cases analyzed for fifty patients with thalassemia major 25 (50%) were female and 25 (50%) male with two main age group above and below ten years' age treated with deferasirox as an iron chelating agent. The oral chelating was started after detection of the level of ferritin in serum > 1000 ng/ml. Those children did not take any other chelation before deferasirox (Figure-1).

The average level of ferritin in serum at the initiation of this study was 2678.83 ng/ml before treatment and 2255.43 ng/ml after deferasirox commenced, with standard deviation 843.654 and 1275.04 before and after treatment, respectively, after follow up of serum ferritin (Table -1 and Figure-2).

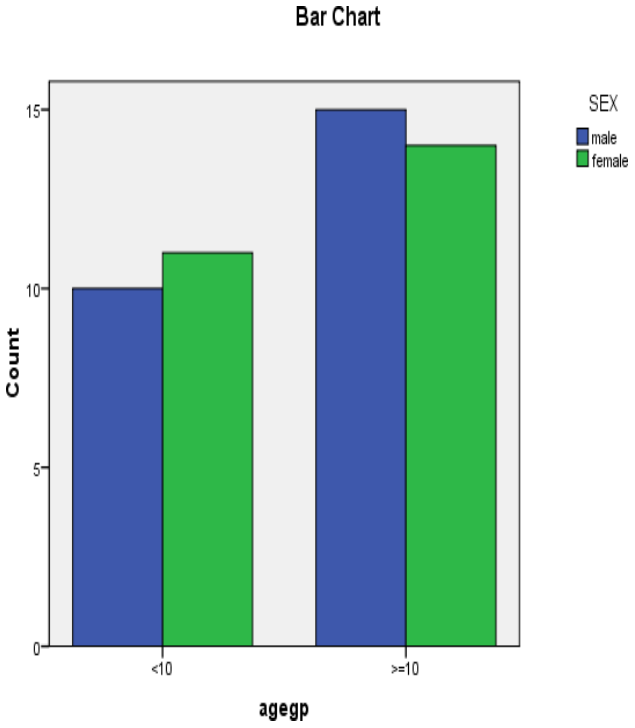

Figure 1: Baseline age and sex of patients

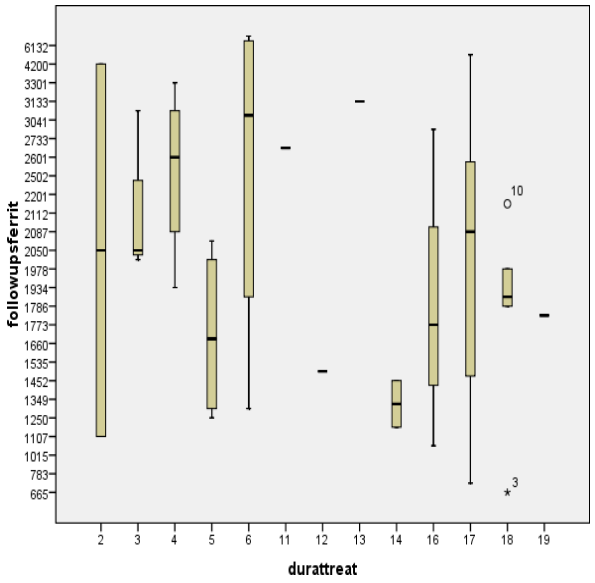

Figure 2: Follows up of serum ferritin after 19 months' treatment

During the follow-up of serum ferritin after treatment in relation to sex, the mean in the male are 2.4320E3 and 2.2554E3 in the female, there is no statistically significant relationship between serum ferritin follow up result and sex as shown in (Table -2). Age of the patient whether above or below 6 years' age 2.4088 and 2.1764 respectively with the same result as shown in (table-3). The study group recorded a good compliance in (35) 70% and poor in (15) 30% (Table-4). Patients treated with deferasirox showed some gastrointestinal symptoms like abdominal cramps, vomiting, and diarrhea in (6) 12% of cases and skin rash in (1) 2% and increase in a liver enzyme in (2) 4% and. No, any patient experienced significant proteinuria or renal function problems during the study period and more than 80% patient with no any adverse effect. Most of the children and their families were a pleasure with the deferasirox because it is easier intake. Figure-3 shows the side effect of deferasirox.

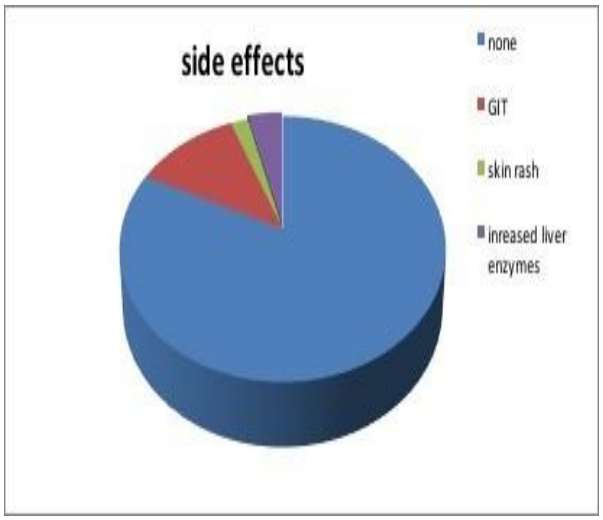

Figure 3: Common adverse effect of deferasirox

Table 1: Serum ferritin before and after deferasirox

	Mean	N	Std. Deviation	p-value
Ferritin level before treatment	2678.83	50	843.654	0.001
Ferritin level during follow up	2255.43	50	1275.04	

Table 2: Relation of serum ferritin with sex

Follow up S.ferritin				
Sex	**Mean**	**N**	**Std. Deviation**	
Male	2.4320E3	25	1290.49353	0.12
Female	2.0787E3	25	1260.59217	
Total	2.2554E3	50	1275.09604	

Table 3: Relation of age group with level of serum ferritin

Follow up S.ferritin			
Age of dx	**Mean**	**N**	**Std. Deviation**
≤6 years	2.1764E3	33	1315.24907
>6 years	2.4088E3	17	1217.20651
Total	2.2554E3	50	1275.09604

Table 4: Compliances of patient with deferasirox

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Good	35	70.0	70.0	70.0
	Non	15	30.0	30.0	100.0
	Total	50	100.0	100.0	--

DISCUSSION

This study occurred at hematology and thalassemia Centre to assess the deferasirox medications effect on serum level of ferritin, a complication of therapy and the compliance of the patients with these type of medications because the iron overload and transfusional hemosiderosis are associated with many problems and death rate in thalassemic patients .The side effect of the drugs in this study differed to data from variable sources ; there is no risky adverse event caused by this drug (Elalfy et al, 2013) . Patients treated with deferasirox showed some gastrointestinal symptoms like abdominal cramps, vomiting, and diarrhea in 12% of cases, skin rash in 2% and increase in a liver enzyme in 4%; however more than 80% patient with no any adverse effect and not require any dose adjustment. Increase in serum transaminase above twice the upper limit of normal was reported in 2 of the 296 patients by Brown et al (2003). Generally, the deferasirox typically well affordable, with a minimal side effect. The gastrointestinal symptoms, including abdominal cramps, vomiting, loose stool, constipation, and nausea occur in approximately fifteen percent of thalassemia patients by (Cappellini et al, 2006). Gastrointestinal problems are the frequent complications that can be treated by changing the time of

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deferasirox intake. Skin lesion or rash occur nearly in ten percent in the same study.

No any patient in the present study experienced significant proteinuria or renal function problem during the time of follow up. In other study liver failure rarely reported, so the hepatic enzyme and liver function test must be checked each about 15 days for the first month after initiation of therapy with this drugs and every four weeks after that. The serum creatinine level increase in 1/3 of patients in the first few weeks of initiation of treatment or after increasing the dose, and reach to an abnormal level in very rare cases (Cappellini et al, 2008). However, the common complications of deferasirox therapy in those patients are cramps in the abdomen, loose stool, regurgitation, increase in the liver enzyme and nausea; however, frequency of these side effect yearly decline from year to year; these side effect can easily treatable with clinical patient follow up by taking the general information about the onset, frequency, duration, and severity. For loose stool and cramps of the abdomen, the hydration of the patients should be maintained and take a simple drug to stop diarrhea for two to three days if required. Patients may change the time of deferasirox intake at the evening instead of the morning. skin rashes occur in minimal to moderate form and spontaneously resolve; however, decreasing the dose or stopping the drugs in severe cases of skin involvement as in study (Taher et al, 2008). A slight increase in serum creatinine may occur and not progressive, However, these increments were depending on the dose involved and spontaneously resolved. The serum creatinine levels are evaluated before and after treatment and every month after that with any increment should be managed by decrease the dose or even stopping the drug; this is in Vichinsky study, unlike our present study (Vichinsky et al, 2008).

The average of ferritin level at the initiation of the study was 2678.83 ng/ml before treatment and 2255.43 ng/ml after deferasirox commenced, with standard deviation 843.654 and 1275.04 before and after treatment respectively after a follow up of serum ferritin as compared to other studies and by Taher et al. (2008). In a study at the hospital of rural West Bengal by Bandyopadhyay et al (2013). The patients in this study showed high serum ferritin levels even in younger early life age group. the average serum ferritin was 1750 ng/ml founded in first five years age group, and this increased to 3650 ng/ ml from eleven to fifteen years age group (Bandyopadhyay et al, 2013).The level of ferritin in serum could not be controlled because the compliances in few patients only with regimen recommended at home (Eleftheriou , 2008) which is Similar to the current study, the average serum ferritin level was 2678.83 ng per ml, which is very higher than the normal acceptable levels for a normal person. The usual reading of ferritin level in serum for male and female are 12-300 ng/ml and 12-150 ng/ml, respectively (Berdoukas et al, 2012). The assessment of hepatic concentration for iron is the correct technique of iron accumulate assessment. But this method is difficult and was not available in our setup. The easiest way is the detection of ferritin level in serum, which is reliable, available and simple to perform, and low cost without complications (Olivieri et al, 1997). Some patient shows a very good response to deferasirox tablet while the others with poor response and the cause remain unknown. Certain data have shown that some patients do not show any negative balance of iron at 40/ kg per day. the data also shown those children with poorly response have a low systemic involvement in comparison with those of good response (P-value <0.00001) (Chirnomas et al, 2009).

The lower value of ferritin levels in serum between1000 to 1500 ng/ml in the present study were put at a dose of 10-20 mg/kg per day at the initiation of deferasirox and those with ferritin levels of > 1500 ng/ml or were put reach to 20-40 mg/kg per day of deferasirox. Cappellini et al, (2008) study showed that doses of (five to ten per kg/ day), the store of the iron increased while at 20 mg per kg /day, a neutral balance of iron possibly neutral. However, the iron balance negatively achieves with at least (30 mg per kg/day), Taher et al. (2008) report this in the other study. The drug integrity at doses equal or more than thirty mg / kg /day showed by (Taher et al,2009). These study also showed the ability to increase the dose of deferasirox to 40 mg/ kg per day without any of adverse complications of the drug. In present study group recorded a good compliance in 70% of the patients and poor in 30%; deferasirox as a chelating agent of iron are single daily regimen medication with a half-life from eleven to nineteen hrs and these properties showed the benefits of this drug (Nisbet et al,2003, Galanello et al, 2003). Another study about the patients complied with deferasirox therapy reach to more than eighty percent (Cappellini et al,2010). Deferasirox as an oral therapy compliance founded superior to other chelating agents like deferoxamine for the treatment of iron accumulation in in repeatedly blood transfusions patients (Vichinsky et al, 2007). In any patient with chronic anemia, the compliance is the first big problems with medications used for iron chelation. The child and his or her family should be educated about the hazards of iron accumulations and should know how the compliance with therapy can prevent the complications of iron overload as happiness and stuck with this drug lead to improve inpatient general condition and improve the action of chelation therapy, and the dramatical improvement in life quality.

CONCLUSION

Deferasirox is well affordable and safe with treatment for a long time and the side effect with this medication may occur, and for that reason, the correct dose therapy is needed to maintain the good clinical response and decreasing the adverse complications of therapy. Generally, the side effect of this therapy decline with time and the frequently common complication seen are the gas-

trointestinal symptom and involvement of skin and increase in the liver enzyme. Deferasirox therapy due to it is a way of intake safety, formulation and effectiveness lead to significant advancements in future for management of various diseases associated overload of iron in chronic diseases.

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