Iron Chelation Therapy in Sickle Cell/Beta Thalassemia Syndrome, a 2 years' Extension Study

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ABSTRACT

Background: Sickle cell-beta thalassemia (HbS/β-thal) is a good example of a mixture of two types of common hereditary anemias in the Middle East and Mediterranean area, and lately throughout the world (because of continuous people movement to different parts of the globe especially western countries). Since iron overload is blamed for most of complications encountered in these patients, it is very important to chelate them effectively and safely, and deferasirox is one of the best approved options up to date.

Objective: To find out the effects of (deferasirox) within these patients on serum ferritin, functions of liver and kidney, platelet count, and major side events.

Type of the study: Retrospective.

Methods: This is a retrospective extension study for 24 months of 23 (out of a total 52) patients suffering from sickle cell-beta thalassemia (HbS/β-thal) whom regularly attending Baghdad Hereditary Anemia Center at Ibn Al-baladi Hospital for their usual medical care. Medical records of those patients were evaluated regarding five major arms including serum ferritin levels (measured every 3 months), liver enzyme alanine aminotransferase (ALT), serum creatinine, platelets count, and major adverse events (all were evaluated on monthly intervals). At the baseline, all the involved patients were ≥ 2 years old, their serum ferritin levels more than one thousand μg/L, with normal kidney function measured through serum creatinine, normal platelet count, normal heart function considered by ≥50% echocardiographic left ventricular ejection fraction (LVEF), and alanine aminotransferase (ALT) levels were less than 5 times the upper normal laboratory limit.

These limitations led to the exclusion of 29 patients from being enrolled, leaving 23 patients on the table of this study. Patients were divided into two bands namely chelation naïve group and previously chelated with deferoxamin. Period of data collection started from 2nd of January 2014 till the 1st of January 2016.

Results: Total patients encountered were 23, 13 of them were males (57%) and the rest (43%) were females as they were 10 patients. All five arms evaluated showed varying degrees of response in reaction to deferasirox treatment, serum ferritin levels decreased progressively and a bit faster in the first year, serum creatinine lowered steadily with less values in deferasirox naïve group of patients, serum alanine aminotransferase (ALT) had an evanescent rise at the starting months, that declined later on. Platelet counts were lower in previously chelated group expressing a gradual increase for both groups of patients. Nausea &/or vomiting were the most frequently faced side effects, and most of them were temporary occurred during the start of treatment and faded away with time either spontaneously or by medical interventions. All these effects were more seen within previously chelated set of patients.

Conclusions: After a completed 24 months of evaluation, (deferasirox) has the ability to decrease iron overload in susceptible patients whatever was their previous chelation status.

Key words: Sickle cell beta thalassemia, Deferasirox, and Iron overload.

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Sickle cell disease (SCD) and β-thalassemia are common genetic diseases caused by the coinheritance of two mutant β-globin alleles (in homozygous or compound heterozygous combination). Both are chronic diseases with considerable morbidity and mortality. (1) These disorders fall into two large groups of b-globin gene mutations that result in either abnormal hemoglobin structure (SCD) or massively reduced/absent production of B-globin chains (B-TM). The clinical manifestations of these inherited disorders typically appear several months after birth, when gene expression switches from the fetal c-globin chain, which forms fetal hemoglobin (HbF), to the adult B^A^-globin chain forming hemoglobin (HbA). (2) In low-income countries, most of the affected children succumb in early childhood, whereas in developed countries, neonatal diagnosis and supportive care have greatly improved survival. However, even with modern and specialized care, life expectancy is still reduced by several decades,(3-5) and quality of life greatly suffers. (6-8) Novel therapeutic approaches are being developed in an effort to move beyond palliative management, but still in the developing countries, iron chelation therapy is the mainstay therapeutic approach. (9) Although genetic
screening and prenatal diagnosis have reduced the incidence of β-thalassemia in selected countries, such as Sardinia and Cyprus, β-thalassemia remains common in many areas of Asia and the Middle East with limited resources for treatment. (10) Given anticipated population growth, the worldwide prevalence of these diseases is expected to rise dramatically over the next century. (11) HbS/β-thalassemia is part of sickle cell syndrome (12), and majority of patients with sickle cell anemia have received repeated blood transfusions by adulthood with Transfusion therapy is likely to further increase in pediatric patients because of recent evidence indicating its ability to prevent organ injury and improve the outcome of complications. (13-15) Deferasirox is an orally absorbed iron chelator that has been developed for the management of transfusional iron overload. Its safety, tolerability and efficacy in reducing body iron burden have been demonstrated in patients with β-thalassemia major and in other chronic transfusion-dependent anemias. (16)

Methods: Medical records of 52 patients with a diagnosis of HbS/β-thalassemia reaching Hereditary Anemia Center at Ibn Albaladi Hospital in Baghdad were examined over 24 months started from 2nd of January 2014 till the 1st of January 2016. Since all patients had usually visiting the above center on a regular monthly intervals with all notes had been written in their medical files by the attending physician, so at the start of data collection, there were some inclusion criteria for patients to take part in this study (taken from hospital files) included that all of them should have been ≥2 years old, serum ferritin levels were at least >1,000 µg/L, red blood cell transfusions status was either frequent or occasional (≤20 units of red blood cells (RBCs) in lifetime), renal function was normal (serum creatinine less than upper normal laboratory limit (UNL)) and platelet count should have been within normal range (150000 - 400000 /mm3).

Left ventricular ejection fraction (LVEF) was noticed before the study period for all patients through an echocardiography and the result of 50% was the minimum acceptable value, to exclude any heart failure. Also liver enzymes; specifically, alanine aminotransferase (ALT) levels were less than five times the upper normal laboratory limit for all patients. Males were 13 in number (57%) and females were 10 (43%). Only 23 patients were succeeded to enter the study after applying the inclusion criteria. There were 23 patients we put into two main categories or groups based on their iron chelation therapy situation, first group was considered as chelation naïve (11 patients (48%)) and the second one was previously chelated patients with deferoxamin (12 patients representing 52%). Serum ferritin was used to evaluate total body iron, collected at the start of the study and then every three months. Alanine aminotransferase (ALT) was used to estimate liver function for all enrolled patients, done from the beginning till the end of the study period on a monthly basis, that was also applied to serum creatinine and platelet count levels. Deferasirox had a baseline dose of 20 - 30 mg/kg/day for the two categories; chelation naïve patients and previously chelated ones, based on number of RBCs transfusions; so that for occasionally transfused cases (less than 20 throughout lifetime) the lowest dose was used which was 20 mg/kg/day, and the highest starting dose of 30 mg/kg/day was used for frequently transfused patients. All side effects mentioned in patients’ medical files on their regular monthly visit were evaluated carefully, as in some instances the attending physician used certain types of therapies to lessen these adverse events, and even deferasirox dose decreased or stopped for a short time (1-2 weeks) before restarted again. All patients were sent for ophthalmologic and audiographic tests on yearly basis. Paired samples test was used for statistical analysis when needed throughout the study results.

Results: Patients’ ages were within the spectrum of 2-25 years old, and the median age of all involved 23 patients was 17 years. Males were 13 (57%) and 47% (10) for females. Talking about (figure 1); we found a steady decrease of serum ferritin in chelation naïve category from less than 2000 µg/L to reach a very good level of around 1000 µg/L, which is associated with a low iron overload. Also that was applied to the other group of previously chelated with deferoxamin, with even a higher baseline ferritin levels of more than 2000 µg/L down to the better level of near 1000 µg/L, as seen in (figure 2). The rate of downward movement of serum ferritin levels was higher during the first year in both figures. This is a good point to get rid of excess body iron as soon as possible.

Doses of (deferasirox) were increased gradually according to Thalassemia International Federation (TIF) guidelines in response to serum ferritin level. (17) The highest doses of deferasirox was needed between 12-15 months of therapy duration, this may mean that the bulk of iron overload was removed within that period in both groups of patients. Using paired samples test, p = 0.000 (Sig. (2-tailed)) for chelation naïve group, which is a highly significant difference (p value < 0.001), leading to a statistically significant decrease in serum ferritin levels at the end of study period. The same is applied to previously chelated category.
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Figure 1: Deferasirox dose & serum ferritin in chelation naïve patients

Figure 2: Deferasirox dose & serum ferritin in previously chelated patients

Figure 2: Serum creatinine in chelation naïve & previously chelated patients

Serum creatinine laboratory levels had lower values in chelation naïve category than previously chelated patients’ group allower the study period, decreased progressively in both groups, and there was a statistical significant drop (p value < 0.001) in serum creatinine levels within each of above categories as p = 0.000 (Sig. (2-tailed)). As shown in (figure 3). Alanine aminotransferase (ALT) as a liver enzyme had also lower laboratory levels in chelation naïve category through the entire period, but both categories had a transient increase within the first six months and then declined gradually, as illustrated in (figure 4). For both categories, there were statistically significant differences (p value < 0.001) in readings of (ALT), each category apartas p = 0.000 (Sig. (2-tailed)).

There were a slight gradual fall in platet counts within first 2 months of study term followed by a progressive increase that reached near starting counts at the end of one year, and in last month the counts were higher than at the beginning. One patient at first month had a low platelet count of less than 20000/mm3. Applying statistical tests, a significant discrimination(p value < 0.001) was resulted in chelation naïve group, and also previously chelated categories regarding platelt counts, p = 0.000 (Sig. (2-tailed)). This is very important issue to decrease the risk of bleeding tendency.

Repeatedly, all platetl counts were with upper values in chelation naïve category at all times than previously chelated set of patients. These are noticed in (figure 5).

Figure 4: Alanine aminotransferase (ALT) in chelation naïve & previously chelated patients

Obviously each drug has its side effects, and regarding deferasirox oral iron chelation therapy; most of adverse effects occurred at the first 2-3 months of treatment, relieved without any interventions or sometimes medications were needed by the attending physician to alleviate the unwanted symptoms. Nausea with or without vomiting had been the major annoying event for more than quarter of previously chelated patients and about fifth of the other group. Most of patients got over these side effects (as they were transient) through their chelation trip. For more information, please refer to (figure 6).

Figure 5: Platele counts in chelation naïve & previously chelated patients
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Although there is a potential renal toxicity in sickle cell-beta thalassemia and sickle cell patients(23), current data confirms the good tolerability of kidney function reflected through serum creatinine throughout study period with only a small percentage (13%) that had a transient creatinine increase, just like other large studies done by Jordan LB and Voskaridou E(21-23), and again the Omani publication had different results which may be due to associated clinical diseases within recruited patients such as diabetes as a co-factor affecting kidney function.(31)

In addition; there are sporadic case reports of acute renal shut down associated with deferasirox use; as said by Grangé S and Brosnahan G. (32,33) Banerjee S reported that liver disease is associated with sickle cell-beta thalassemia patients (34), but this study found opposite results except for the mild increase in liver enzyme alanine aminotransferase (ALT) levels during first half of first year, which was in line with other studies performed in Europe by Jordan LB and Vichinsky E. (21,22) Whenever there is an iron overload, there are high levels of (ALT) enzyme, which might explain that non-persistent initial increase in our involved patients (35), but later on when deferasirox chelated more liver iron, it would show a better function results, just like what Halawi R and other experts have said very recently. (36) On the other hand, (ALT) levels had a forward decrease after using deferasirox as in Voskaridou E study(23), and that may be related to degree of iron overloading the liver which could be measured by an MRI (magnetic resonance imaging) technique through LIC (liver iron concentration), that was not available widely for Iraqi patients.

Excluding one case of sever thrombocytopenia, there were normal platelet counts, in harmony with other authors like Jordan LB and Lee JW. (21,37)

Most of reported adverse events were either mild or transient appeared majorly in first few months of therapy and faded over time. Nausea, vomiting, diarrhea, skin rash, and abdominal pain were the most commonly noted. This was also mentioned by Vichinsky E and Cappellini MD. (22,38) Based on data collected within current study, chelation naïve group had always better outcomes than previously chelated patients for all parameters tested, and that was also said by Gattermann N. (39) According to the author of this study, there are no publishes yet talking about chelation naïve cases in comparison with previously chelated group, and more follow up data may be needed to get full evaluation of iron chelation therapy in these patients. As a conclusion from present data gathered over an extension of two years, deferasirox is an oral iron chelation drug has the ability to decrease total body iron overload reflected by serum ferritin, with no or little major adverse events either from laboratory or clinical point of view.

References:

Figure 6: Side effects in chelation naïve & previously chelated categories

Discussion: Deferasirox as an iron chelation therapy used in the treatment of patients with sickle cell beta thalassemia (HbS/β-thalassemia) regularly visiting Hereditary Anemia Center at Ibn Albalai Hospital is the major issue of this study, as it was approved by FDA (Food & Drug Administration) since 2005 for treatment of transfusional-dependent and non transfusional-dependent chronic iron overload(18,19)

The above drug was in first use in Iraq since October 2010, and it was considered as one of the earliest countries within Middle East that introduce Deferasirox in their medical practice, given to all patients free of charge.(20)

Iron overload may play a vital role in augmenting the morbidity and mortality of patients with HbS/β-thalassemia(21-23), also the same for other thalassemia types (24-26), as sickle cell-beta thalassemia (HbS/β-thal) is regarded as part of sickle cell disease. (12) Deferoxamine (DFO) was used alone for a long time in Iraq, it is an iron chelation therapy, but because of its parenteral route, compliance is an issue. (16,27) It was a real upgrade for patients to use deferasirox, a once daily oral iron chelating therapy replacing all sufferings brought by previous drug injections. (28) Serum ferritin reflects iron body stores, and iron overloaded patients have higher levels of ferritin.(29) After using deferasirox for 2 years in sickle cell-beta thalassemia (HbS/β-thal) patients, serum ferritin levels declined progressively lowering iron body burden; although these results were found also by other long term studies with a high number of patients such as Jordan LB and Cancado R (21,30), but a study from Oman done by Murtadha Al-Khabori and his colleagues did not agree, may be because of its limited patients enrolled, and it was a single center study unlike the international multicenter above data.(31)


23. Voskaridou E, Plata E, Douskou M, Sioni A,


