Deferoxamine vs. Deferasirox in the Treatment of Thalassemia Major with Iron Overload: Retrospective Study in Thalassemia Center, Kirkuk, Iraq.

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Abstract:

Background: Iron overload is a major problem in patients with Thalassemia major. An effective and safe iron chelator protocol with high compliance rate plays an important role deciding the best treatment option in these patients. This study was done to assess the efficacy and safety of both Deferoxamine and Deferasirox in Thalassemia major patients in Kirkuk province, Iraq.

Patients and methods: In this retrospective study we have included serum ferritin records of 280 Thalassemia major patients treated with two types of iron chelating therapy at Thalassemia center, Azadi teaching Hospital, Kirkuk province, Iraq. The study started since March 2012 till December 2012 and they were categorized in to two groups; First group Thalassemia major patients who had been treated with subcutaneous (SC infusion) Deferoxamine, while second group had been treated with oral Deferasirox (Exjade) with serum ferritin records of both base line and 9 month later had been compared. Most patients with relatively high serum ferritin had been treated with SC Deferoxamine. As a secondary end point, side effect profile had been analyzed in the two studied groups.

Results: 173 Thalassemia major patients (mean age 11 year) treated with oral Deferasirox (Exjade) had mean decrease in their serum ferritin after 9 month was 840 ng/ml while the mean decrease in the 107 patients (mean age=17 year) treated with SC infusion Deferoxamine was (1527 ng/ml) with very significant difference between the two studied groups and (p-value = 0.0005). Abdominal cramp, nausea and vomiting, skin rash were more with oral Desferosix (Exjade) than SC Deferoxamine treated patients [52 (30%), 62 (35%), 13 (7%) versus 23 (21%), 11 (10%), 0 (0%) consecutively]. Renal impairment especially elevation of serum Creatinine to a degree requiring dose modification were found in 15 patients treated with oral Deferasirox (Exjade) while it has not been noticed in patients treated with Deferoxamine.

Conclusion: In spite of less side effects and more compliance of Thalassemia Major Patients treated with Deferasirox than Deferoxamine; Deferoxamine still is more effective treatment modality than Deferasirox in decreasing serum ferritin level.

Keywords: Thalassemia Major, Deferoxamine, Deferasirox, Serum ferritin, Kirkuk, Iraq.

Introduction:

Iron chelating therapies are indicated in hematology to decrease the effect of iron overload on the morbidity and mortality of common hematologic problems like Thalassemia, myelodysplastic syndrome and sickle cell anemia [1]. The two iron chelators that are available parenteral Deferoxamine (Desferal) and oral Deferasirox (Exjade) have got great benefit in decreasing the risk of cardiac problems, congestive heart failure, endocrinopathies, hepatic fibrosis and death, but still these drugs have got their

controversies regarding tolerability and side effect profile [1, 2] .

Patients and methods:

Using SPSS 17 independent t test in this comparative study, we analyzed the data of (280) Thalassemia major patients treated with two types of iron chelating therapy at Thalassemia center, Azadi Teaching Hospital, Kirkuk province, Iraq since March 2012 till December 2012. Patients were categorized into two groups; First group Thalassemia major patients had been treated with subcutaneous Deferoxamine (40 mg/kg/day) 5 days per week infusion over 10-12 hours daily using an infusion pump, while second group had been treated with oral Desferosix (Exjade) [30mg/kg/day which is reduced to 20 mg /kg/day when needed]. In this study Deferasirox oral chelating therapy was used for patients serum ferritin levels less than 4000 ng\ml, while patients with relatively high serum ferritin had been treated with subcutaneous Deferoxamine.

Age categorization into three groups including those who are less than 5 years old, between 5-10 years old and those who are older than 10 years old with comparison in between the two groups of patients on Iron chelating therapy was. Furthermore, side effects between the two groups had been analyzed including abdominal pain, asthenia, skin rash, conjunctivitis, nausea and vomiting, dyspepsia and others like headache.

Results:

(173) Thalassemia major patients treated with Exjade have a (mean age of 11 years) at the start of the study with male to female ratio (1:1.16) and mean baseline serum ferritin of 2680 ng/ml which had Despite the lack of data on long term effectiveness, most patients now make use of Deferasirox because of the ease of oral administration [3]. Deferasirox is also preferred for prophylactic or maintenance therapy [4]. Deferoxamine, which has been proved to reverse iron-induced heart disease and increase long-term survival, may be indicated if Deferasirox is ineffective in a particular patient, and it may be favored for severe iron overload, especially with cardiac involvement [5]. Measuring serum ferritin alone as an indicator for iron burden had some disadvantages as an indirect measure for iron burden and not reflecting accurately the iron status in organs like liver and heart e, also serum ferritin levels fluctuate in their response to inflammation, abnormal liver function and ascorbate deficiency. Now a day, many new advanced techniques had been adopted for more accurate estimation of Iron burden in Thalassemia major patients like liver biopsy, liver MRI, cardiac MRI T2*. In spite of that, serum ferritin seems to have some advantages like being inexpensive, easy to done, positively correlate with morbidity and mortality and still it is adopted in many Thalassemia centers as a useful mode of monitoring iron chelating therapy [6, 7, 8]. decreased over 9 month to a mean of (840 ng/ml).The second group of Thalassemia major patients (n=107) had been treated with subcutaneous Deferoxamine (mean age of 17 year) with male to female ratio (1:1.31), and mean base line serum ferritin of 5670 ng/ml decreased to 1527 ng/ml after treatment with the subcutaneous Deferoxamine (Figure 1). Crossover from one iron chelating therapy to another has been allowed and 21 patients treated with subcutaneous

Deferoxamine had changed to Exjade while 5 patients had changed their therapy to Deferoxamine.

By comparing the two populations of patients in three age groups sub categorization we can see that most of those who are on Deferoxamine are more than 10 years old age; while the rest are in the age group of (5-10 years old) and none of the patients is less than 5 years old age. While those Thalassemia major patients who are on Exjade have got similar distribution in three age categories as seen in (figure 2). Male to female ratio shows slight female predominance in both Exjade and Deferoxamine (Desferal) as shown in (figure 3).

Using independent two sample t-test and comparing the two mean decrease serum ferritin following iron chelating therapy, shows significant difference between the two group and p-value = 0.0005, which is very significant. (Table1).

Side effects have been recorded in the two studied group concentrating on abdominal cramp, nausea and vomiting, skin rash, asthenia, allergic conjunctivitis, dyspepsia and even the effect of both drugs on the renal function test. Abdominal cramp, nausea and vomiting, skin rash were more in Exjade than Deferoxamine treated patients (30%, 35%, 7% versus 21%, 10%, 0% consecutively).Fifteen patients treated with Exjade had an increase in their serum creatinine to limits requiring dose modification while there was no renal impairment in patients treated with subcutaneous Deferoxamine, (table 2).

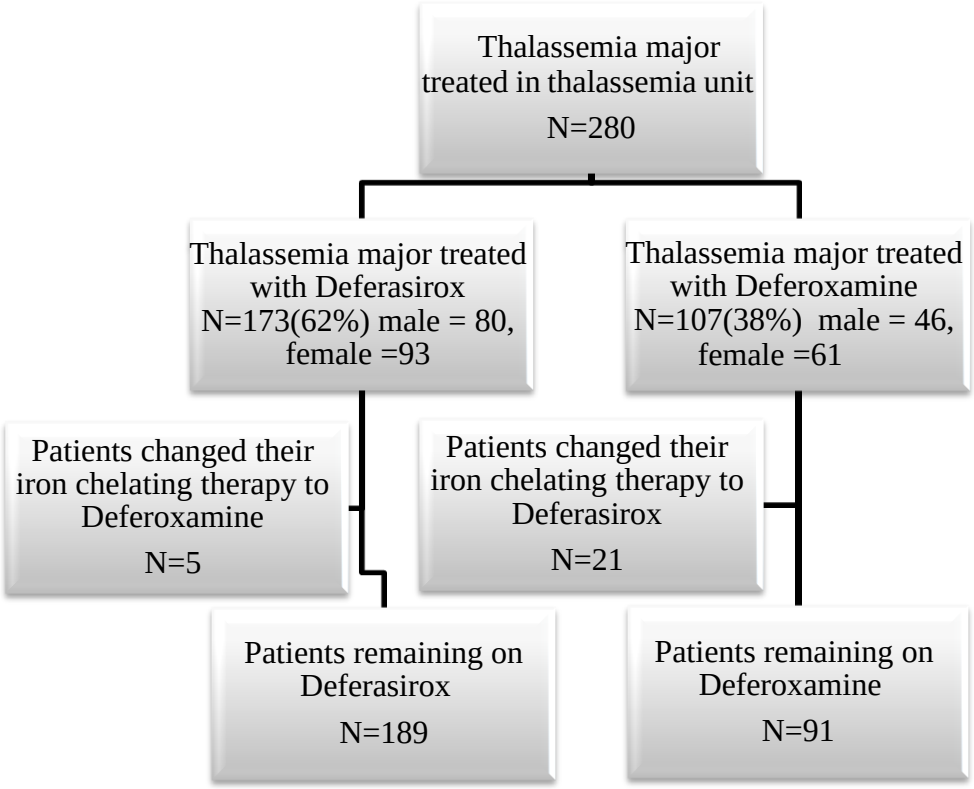

Figure (1): Censor diagram for thalassemia major patients treated with two types of Iron chelating agent over 9 month.

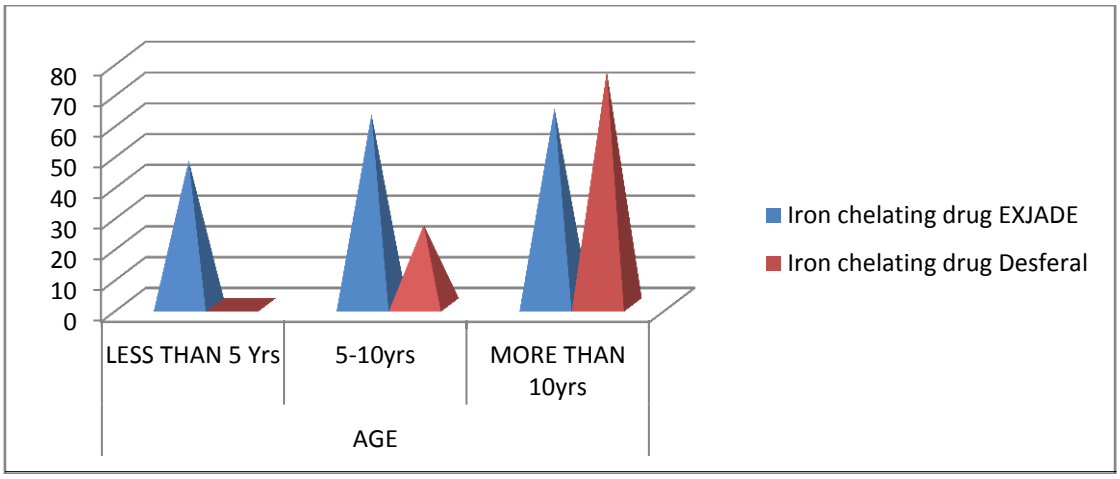

Figure (2): Comparison between Deferasirox (Exjade) and Deferoxamine (Desferal) in three categories of age group.

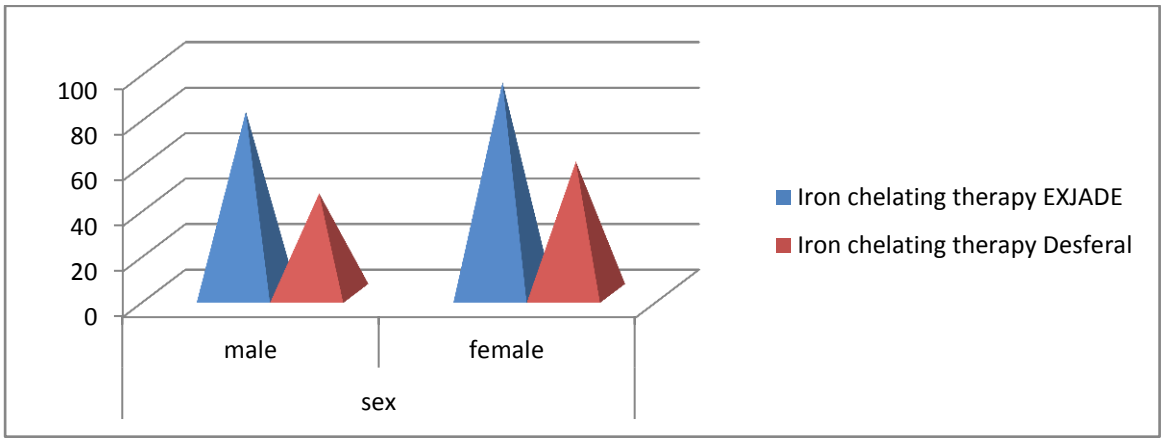

Figure (3): Sex differences in both Deferasirox (Exjade) and Deferoxamine (Desferal) Group.

Table (1): Statistics for the mean difference in the serum ferritin after treatment with Iron chelating therapy.

Iron Chelating therapy	No. of patients	Mean difference in Serum ferritin	Standard Deviation	Standard error Mean	*P* value
Deferasirox	173	840.5723	1036.40	78.79	0.0005
Deferoxamine	107	1527.5294	681.62	67.49	

Table (2): Difference in the side effect profile between the patients treated with Deferasirox (Exjade) and Deferoxamine (Desferal).

Side effect type	Oral Exjade n=168	SC* Deferoxamine n=86
Abdominal cramp	52 (30%)	23 (21%)
Skin rash	13 (7%)	0
Nausea and vomiting	62 (35%)	11 (10%)
dyspepsia	18 (10%)	2 (1.8%)
Elevated Serum creatinine to upper limits	26 (15%)	0
Asthenia	54 (31%)	17 (15%)
headache	38 (21%)	22 (20%)
Allergic conjunctivitis	15 (8.6%)	0

*Subcutaneous

Table.3 Difference in the rate of main sides for Oral Deferasirox between our study and Capellini et al study [13].

Side effect	Our study	Capellini et al [13]
Abdominal cramp	30%	13%
Skin rash	7%	5%
Nausea and vomiting	35%	22.5%
Elevated serum creatinine	15%	38 %

Discussion:

In this retrospective study we evaluate the effect of iron chelating therapy (Deferoxamine or Deferasirox) on serum ferritin in Thalassemia major patients as a primary end point.

Deferasirox is an effective oral iron chelator with a long half-life, which could be used as monotherapy. However, the efficacy on the high iron overload is questionable; in addition to that it could not achieve a negative iron balance even with highest recommended dose, which might cause severe side effects [9, 10, 11, 12]. For those reasons patients with high serum ferritin (above 4000 ng/ ml) were preferred to be given SC Deferoxamine.

Capellini et al [13] were the pioneers for using oral Deferasirox as a monotherapy in Thalassemia major patients and prove the non-inferiority to subcutaneous Deferoxamine in Thalassemia major patients. Although, in their study they use Liver Iron content (LIC) as a mean for the burden of iron and monitoring response to therapy, still they consider changes in Liver Iron Content (LIC) parallel to changes in serum ferritin. Comparing the mean decrease in serum ferritin level in our study (for both irons chelating group) with the results in Capellini et al study [13]; we can see that (mainly in patients with Liver Iron Concentration more than 14 mg Fe /g dry weight) the decrease in serum ferritin level over one year study period was1003ng /ml in Deferoxamine group Capellini study, and in our study was 1527 ng/ml while 926 ng/ml in Deferasirox group-Capellini study, while in our study it was 840 ng/ml. This means nearly similar effects for both irons chelating therapy on serum ferritin in our study to Capellini et al study.

As the oral Deferasirox become available just in the last decade in our center and show less side effect profile and more compliance with the patients in comparison to SC Deferoxamine (which require SC an electronic pump for slow infusion over 8-12 hours, 5 to7 nights per week), so we can notice from the age sub categorization that most Thalassemia major patients treated with SC Deferoxamine were in the age group more than 10 years old age and just (20%) in the age limit 5-10 years old and even non in the age group less l than 5 years. This is because the oral Deferasirox becomes available in our center and it shows more compliant by patients in comparison with subcutaneous Deferoxamine [14].

Sex ratio analysis illustrates slight female predominance over male similar to a study done at Italy [15]. While in a study done in a nearby Mosul province between 2001and 2002 there was slight higher male to female proportion (54%:46%) [16].

Crossover between the two therapies lines had been allowed as five patients in the Deferasirox group changed their treatment to Deferoxamine at higher levels of serum ferritin monotherapy,

while 21 patients on the subcutaneous therapy did not tolerate the infusion pump and change to oral Deferasirox. The cross over allowance based on studies preferring either combination or sequential Iron chelating therapy over monotherapy for more compliance and optimal 24 hour chelator "coverage" [17, 18, 19, 20, 21].

Regarding the side effect profile for oral Deferasirox in comparison with Capellini et al data [13] we can see that skin rashes take place in nearly similar rates, while abdominal cramps, nausea and vomiting seems to be more profound in our study. Affecting the renal function and elevation of serum creatinine to high levels during the Deferasirox was less in comparison with Capellini study (table 3).

Conclusion:

In spite of less side effects and more compliance of Thalassemia Major Patients treated with Deferasirox than Deferoxamine; Deferoxamine still is more effective treatment modality than Deferasirox in decreasing serum ferritin level.

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