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A Randomized Comparison of Deferasirox Versus Deferoxamine for the Treatment of Transfusional Iron Overload in Patients with ß-Thalassemia Major in Upper Egypt

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ABSTRACT

Background: Many patients with transfusional iron overload are at risk of progressive organ dysfunction and early death. Poor compliance with iron chelators is believed to be a major contributing factor.

Objective: The aim of this study is to evaluate the efficacy of deferasirox in comparison with deferoxamine for the treatment of transfusional iron overload in patients with ß-thalassemia major in Upper Egypt.

Patients and Methods: A prospective study was designed to evaluate once-daily deferasirox (Exjade) for 48 weeks in 44 patients diagnosed as ß-thalassaemia major ≥2 years old with iron overload that previously either had received no chelating agent or chelated with deferoxamine. Most patients began treatment with deferasirox 10mg/kg /day and may be increased to 30mg/kg/day. Serum ferritin level was assessed before and after beginning of deferasirox (Exjade) treatment at 3 months interval for 48 weeks.

Results: Adverse events, most commonly associated with deferasirox, were mild including transient nausea, vomiting, diarrhea, abdominal pain and skin rash. The mean serum ferritin level had significantly decreased in all ß-thalassaemia major patients with iron overload treated with deferasirox compared to those on deferoxamine.

Conclusion: Administration of Exjade therapy as an oral drug is considered to be preferable and more effective than the parentral iron chelating therapy in the Upper Egypt due to the poor patient compliance and poor practical regimen of parenteral infusions.

Key Words: *ß-thalassemia major – Iron overload – Deferasirox – Deferoxamine.*

INTRODUCTION

Chronic iron overload is a serious complication of the repeated blood transfusions that are necessary for the treatment of patients with blood disorders such as thalassemia, sickle cell disease (SCD), myelodysplastic syndromes (MDS) and various other rare anemias, including aplastic anemia (AA). Without chelation therapy, humans are unable to eliminate the iron released from the breakdown of transfused red blood cells and the excess iron is deposited as hemosiderin and ferritin in the liver, spleen, endocrine organs and myocardium, leading to organ failure, particularly of the liver, heart and endocrine glands **[1,2]**. Diverse manifestations of iron overload are commonly seen in regularly transfused children and adolescents with B-thalassemia. These may include growth impairment and delayed sexual maturation due to impaired pituitary function, diabetes mellitus due to damage to pancreatic islet cells, and cardiac complications later in life **[3]**.

Morbidity and mortality in regularly-transfused thalassemia patients are due primarily to the effects of iron overload rather than to the underlying disease, with over half of all deaths attributable to cardiac complications **[4]**. Following extensive clinical research in the management of iron overload, patients with thalassemia major receiving effective chelation therapy were found to have significant improvements in survival **[4]**. Iron chelators mobilize tissue iron by forming soluble, stable complexes that are then excreted in the feces and/or urine **[5]**.

Iron overload can be effectively managed by adequate chelation therapy as documented by experience with deferoxamine (Desferal®, DFO), which has been in clinical use for more than 40 years and is the current reference standard chelating agent **[6]**. The poor oral bioavailability and short plasma half-life of DFO necessitates parenteral administration and prolonged

infusions. The standard regimen to remove excess iron accumulated through regular transfusion is a subcutaneous (SC) infusion over 8-12 hours, on 3 to 7 days each week. This inconvenient schedule has a negative impact on compliance and eventually on long-term outcome, with some deaths being directly attributable to poor compliance with therapy **[7,8]**. Poor compliance to deferoxamine therapy is even more pronounced among adolescents **[9]**.

There is, therefore, a clear requirement for an effective, well-tolerated iron chelator with a less demanding mode of administration to ensure patient compliance to life-long chelation therapy in transfusion-dependent anemia.

Deferasirox (Exjade®, ICL670), an N- substituted bis-hydroxyphenyl-triazol was selected from more than 700 compounds as part of a rational drug development program **[10]**. Deferasirox represents a new class of tridentate iron chelators with a high specificity for iron **[11]**. In prior studies evaluating the efficacy and safety of deferasirox, dosing was based on baseline liver iron concentration (LIC) as assessed by either liver biopsy, superconducting quantum interference device (SQUID) or magnetic resonance imaging (MRI) **[12]**. Biopsies are uncomfortable for the patient, particularly the elderly, and can lead to complications such as bleeding and infection, especially in MDS or AA patients with hemostatic impairment **[13]**. The consistency of results obtained from studies measuring the accuracy of LIC by SQUID is generally poor, with the underestimation of SQUID-determined LIC compared with biopsy-determined LIC being a critical factor **[8]**. Measurement of LIC by MRI is not used routinely as it requires special software and expertise and is often unavailable or relatively expensive in many regions worldwide. Hence, serum ferritin concentration remains a convenient, less expensive and widely used way of assessing body iron and, when followed serially, is a suitable alternative marker of trends in body iron burden as significant correlations between changes in LIC and serum ferritin have been identified in various types of anemia **[14]**.

PATIENTS AND METHODS

Eligibility and enrolment procedures:

The patients were divided into two groups, group (I) included 15 patients (11 males and 4 females) (≥2 years old) with ß-thalassaemia major and transfusional iron overload who required ≥8 blood transfusions /year and had a serum ferritin level of ≥1000ng/mL with no iron chelating therapy before, while group (II) included 29 ß-thalassaemia major patients (19 males and 10 female) (≥2 years old) had a serum ferritin level of ≥1000ng/mL and treated with prior mono or combination therapy with deferoxamine and/or deferiprone but had experienced unacceptable toxicity to deferoxamine, had poor response despite proper compliance with deferoxamine, had documented non-compliance of taking <50% of prescribed deferoxamine doses in the previous year or if deferoxamine treatment was contraindicated.

All patients commenced deferasirox at a dose of 10mg/kg/day, the lowest dose of the therapeutic range reported in previous studies **[2]**. Deferasirox was administered once daily, 30 minutes before breakfast, and doses were dispersed in a glass of non-carbonated bottled water and ingested immediately.

Blood transfusions were regularly administered during the study period according to the patients' requirements with the aim of maintaining haemoglobin level ≥8g/dL.

Safety assessments: Laboratory assessments were performed at monthly intervals and included complete blood counts, serum gamma-glutaryl-transferase, total protein, urea and creatinin. Also, Iron parameters including total iron and serum ferritin were assessed at 3 months interval for 48 weeks during the study and the change was determined using the baseline and final ferritin levels.

Patients were excluded from the study if they had a mean alanine aminotransferase and/or serum creatinin above the upper limit of normal, significant proteinuria, uncontrolled hypertension, chronic hepatitis B or active hepatitis C receiving specific treatment and/or a history of nephrotic syndrome or any medical condition that may affect absorption, distribution, metabolism or excretion of deferasirox. Patients were also excluded if they had a history of noncompliance either with treatment or the protocol (e.g. patients who were considered potentially unreliable and/or not cooperative).

Statistical methods:

Data were analyzed and expressed as mean values±standard deviations (SD). SPSS version 16 program was used for data processing. One Way ANOVA was used in comparison of numerical data. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

This study included 44 ß-thalassemia major patients with iron overload, 30 males and 14 females; their ages ranged from 2 to 15 with a mean of 6.9±4.1 and a median of 6 years. Adverse events, most commonly associated with deferasirox, were mild including transient nausea, vomiting, diarrhoea, abdominal pain and skin rash. The gastrointestinal adverse events that patients experienced with deferasirox were generally transient in nature and lasted about 1 week maximum. They are all transfusion dependant with rate of transfusion ranging from 6 to 25 times per year (13.5±4.4). Six patients from the 44 patients were splenectomized (13.6%), 10 patients were Hepatitis C antibodies positive (22.8%) one patient was Hepatitis B positive (2.27%) and two patients were positive for both C and B viruses (4.54%).

Prior to deferasirox therapy, the patients were divided into two groups, group (I) did not receive any form of iron chelation before while group (II) were on iron chelatores deferoxamine and/or deferiprone; their demographic data are summarized in Table (1). Follow-up serum ferritin level was measured every three months after Exjade therapy, in which there was a significant decrease of the mean serum ferritin level after (3,6,9,12) months of initiation of therapy when compared to that before Exjade therapy in both groups (Table 2, Figs. 1,2).

Table (1): Demographic data of 44 ß-thalassemia major patients prior to Exjade therapy.

Variable	Group (I) n=15	Group (II) n=29
Age in years	2-4 (3±.6547)	2-4 (3±.6547)
Gender:		
Male	11(25%)	11(25%)
Female	4 (9%)	4 (9%)
Packed RBCs Transfusion per year	6-15 (10.7±3.2)	6 -15 (10.7±3.2)
Splenectomy	0	0
Base line serum ferritin ng/ml	1646.67±528.97	1646.67±528.97

Group (I) : Did not receive any form of iron chelation before.
Group (II): Were on iron chelatores deferoxamine and/or deferiprone.

Table (2): Base line serum ferritin level (ng/mL) before and at 3,6,9 and 12 months after Exjade therapy in 44 ß-thalassemia major patients.

Variable	Serum Ferittin				
	Base line	3 months	6 months	9 months	12 months
Group I: (No: 15)	1646.66±528.97*	1603.33±537.68	1486.67±479.38	1360±418.84	1176±457
p-value**		0.01	0.001	0.001	0.001
Group II: (No: 29)	2131.03±374.26	2044.83±365.1	1858.62±338.60	1675.86±336.63	1541.38±328.98
p-value**		0.001	0.001	0.001	0.001

* Mean ± standard deviation.
***p*-value: Serum ferritin levels after vs. before Exjade therapy.
Group (I) : Did not receive any form of iron chelation before
Group (II): Were on iron chelatores deferoxamine and/or deferiprone.

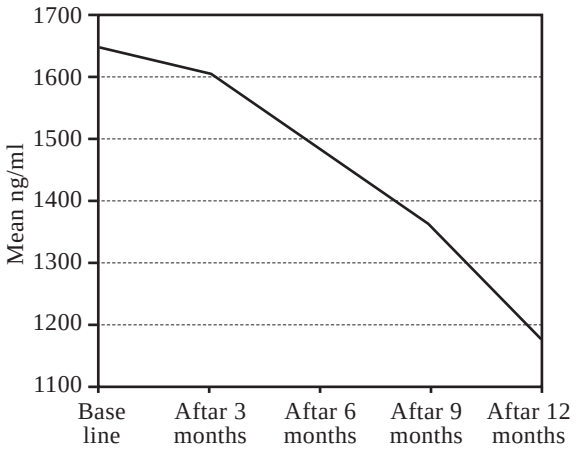

Fig. (1): Serum ferritin level before and after. Exjade therapy in Group (I) patients.
(Did not receive any form of iron chelation before)

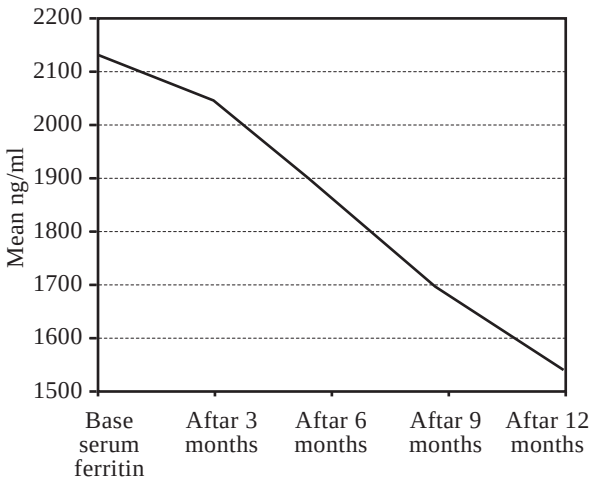

Fig. (2): Serum ferritin level before and after. Exjade therapy in Group (II) patients.
(Were on iron chelation deferoxamine and/or deferiprone)

DISCUSSION

Chronic iron overload due to blood transfusions leads to significant morbidity and early mortality unless adequate chelation therapy is administered. Deferoxamine is the reference chelation therapy that has a well-established safety and efficacy profile. Patients who are treated adequately with deferoxamine from early on in life do not develop typical complications of iron overload, including cardiac, endocrine, and hepatic failure **[15]**. However, because deferoxamine must be administered by prolonged subcutaneous or intravenous infusion, patient acceptance of and compliance with therapy are often poor. So, despite the availability of an effective chelating agent, the compliance issues with deferoxamine mean that many patients still develop clinically significant iron overload, with the related impact on morbidity and mortality.

In prior studies evaluating the efficacy and safety of deferasirox, dosing was based on baseline liver iron concentration (LIC) as assessed by liver biopsy **[12]**. Biopsies are uncomfortable for the patient, and can lead to complications such as bleeding and infection **[13]**. The measurement of LIC by MRI is not used routinely as it requires special software and expertise and is often unavailable or relatively expensive. Hence, serum ferritin concentration remains a convenient, less expensive and widely used way of assessing body iron and, when followed serially, is a suitable alternative marker of trends in body iron burden as significant correlations between changes in LIC and serum ferritin have been identified **[14]**. These findings support the use of regular serum ferritin assessments for the monitoring of deferasirox therapy **[16]**. In the current study, we used serial serum ferritin levels to assess body iron level in thalassemic patients.

Our results are in agreement with Cappellini et al. **[14]** who stated that the compliance with the administration of parenteral deferoxamine chelation therapy has proved challenging to all groups of patients with transfusional iron overload.

Deferasirox was developed in response to the need for an oral iron-chelating agent. In particular, it was desirable to have an agent that could be administered conveniently to patients of all ages, and across a range of iron burdens. Previous clinical studies indicated the potential of deferasirox to meet this need **[17]**. This current study was performed to compare this agent to deferoxamine. Because complications of chronic iron overload have been best studied in thalassemia, this population of patients was used for the demonstration of efficacy for deferasirox.

A significant decrease in serum ferritin levels was observed in our study after the usage of deferasirox; these results are consistent with the studies of Nisbet et al. **[18]** and Cappellini et al. **[14]** in their previously published short-term study examining the ability of deferasirox to remove iron from the body.

The same finding was observed in Porter **[1]** study who reported that the effective adminis-

tration of iron chelation therapy has been limited by the route of its administration. Although deferoxamine is effective in removing iron from the body, yet due to very poor oral bioavailability and a short half-life it must be administered by subcutaneous or intravenous infusion; the compliance with this regimen is often poor. Also Treadwell et al. **[19]** had reported that the availability of a once-daily, oral alternative deferasirox would potentially facilitate improved compliance, and thereby reduce morbidity and mortality from iron overload.

Also our results are in agreement with Elliott et al. **[20]** and Stumpf **[21]** as they reported that in routine clinical practice, compliance with a once-daily, oral regimen offers a promising alternative for patients unwilling or unable to comply with parentral deferoxamine therapy.

Conclusion:

In conclusion, these data provide evidence that patients with ß-thalassaemia major with iron overload may be effectively managed using deferasirox regimen and considered to be preferable and effective than the parenteral iron chelating therapy due to the poor patient compliance and poor practical regimen of parenteral infusions especially at our locality.

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