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Comparison of deferasirox and deferoxamine effects on iron overload and immunological changes in patients with blood transfusion-dependent β-thalassemia

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Abstract:

INTRODUCTION: Beta-thalassemias are a cluster of inherited (autosomal recessive) hematological disorders prevalent in the Mediterranean area due to defects in synthesis of β chains of hemoglobin. The aim of present study was to compare the effects of deferasirox and deferoxamine on iron overload and immunological changes in patients with blood transfusion-dependent β-thalassemia major and intermedia.

PATIENTS AND METHODS: This study involved 64 patients with known cases of β-thalassemia major or intermedia that has been treated with blood transfusion and iron chelators. Serum ferritin, serum iron, serum total iron binding, unsaturated iron-binding capacity (UIBC), and immunological parameters were assessed in deferoxamine and deferasirox-treated patients.

RESULTS: In deferoxamine-treated patients, serum ferritin levels were high (8160.33 ± 233.75 ng/dL) compared to deferasirox-treated patients (3000.62 ± 188.23 ng/dL; $P < 0.0001$), also there were significant differences in serum iron, total iron-binding capacity and UIBC ($P < 0.0001$) in deferasirox-treated patients compared to deferoxamine-treated patients. Immunological changes between two treated groups showed insignificant differences in levels of complements (C3 and C4) and immunoglobulin levels (IgM, IgG, and IgA) $P > 0.05$.

CONCLUSION: This study indicated that deferasirox is more effective than deferoxamine regarding the iron overload but not in the immunological profile in patients with blood transfusion-dependent β-thalassemia.

Key words:

Deferasirox, deferoxamine, serum ferritin, β-thalassemia

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Beta-thalassemias are a cluster of inherited autosomal recessive hematological disorders prevalent in the Mediterranean area due to defects in synthesis of β chains of hemoglobin, caused by mutation in the HBB gene on chromosome 11 leading to from asymptomatic to clinically severe hypochromic microcytic anemia.[1]

The types of beta-thalassemia are major, intermedia, and minor depending on hemoglobin type and clinical presentations that include splenomegaly, hemolytic anemia, jaundice, and gallstones, those only seen in major and intermedia types, while in beta-thalassemia minor the clinical presentation is mainly misdiagnosed as iron deficiency anemia that was refractory to iron therapy.[2]

Beta-thalassemia minor treated with folic acid only and rarely need a blood transfusion, while beta-thalassemia major and intermedia are blood transfusion-dependent types, since untreated beta-thalassemia leads to congestive heart failure and eventually to death.[3] Repeated blood transfusions lead to iron overload and toxicity causing cardiac siderosis, pulmonary hypertension, and endocrinopathy.[4] Therefore, iron chelating therapy is mandatory to prevent iron overload-induced complications accordingly, iron chelators such as deferoxamine, deferiprone, and deferasirox are used with repeated blood transfusion in the management of anemia in beta-thalassemia major and intermedia.[5]

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The first iron chelator was deferoxamine derived from *Streptomyces pilosus* which introduced in 1960, administrated parenterally (intravenous [IV] or subcutaneous [SC] but not intramuscular) with short half-life and dose-dependent effect.[6] SC administration of deferoxamine leads to severe pain at site of injection, while prolonged IV administration leads to noncompliance; also, frequent deferoxamine administration causes growth retardation,[7] thus, the necessity for oral iron chelator is required like deferiprone and deferasirox.

Deferiprone is the first oral iron chelator, and it is a bidentate hydroxypyridone introduced in the year 1980 for management of iron overload through binding with iron and the complex will excreted in the urine;[8] deferiprone has relatively short half-life due to rapid hepatic metabolism and given in a dose of 75 mg/kg/day with significant lowering of intracellular iron overload.[9] Deferiprone leads to many adverse effects such as agranulocytosis due to myelotoxicity, gastric upsets, liver damage, and arthralgia.[10]

Deferasirox is a new oral iron chelator introduced in 2005 for the management of iron overload in beta-thalassemia major and intermedia. Deferasirox has high plasma protein binding with long half-life and metabolized by liver with subsequent fecal excretion.[11] It is more effective than deferiprone in the treatment of iron overload even in sickle cell anemia with relatively less adverse effects compared to deferiprone, but it causes transient acute renal insufficiency.[12]

Moreover, beta-thalassemia major and intermedia are associated with several immunological disorders due to defect in phagocytosis, opsonization, lymphocyte functions, and immunoglobulin levels;[13] these changes were linked to the iron overload, splenectomy, and recurrent exposure to the foreign antigens through repeated blood transfusion.[14]

Therefore, the aim of present study was to compare the effects of deferasirox and deferoxamine on iron overload and immunological changes in patients with blood transfusion-dependent beta-thalassemia major and intermedia.

Patients and Methods

This study was done in the Department of Clinical Pharmacology and Therapeutic, College of Medicine, Al-Mustansiriya University in cooperation with Iraqi Center of Hematological Diseases and Research in Baghdad, Iraq, from June to December 2015. This clinical patients-based study was done according to the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects.[15] This study was approved by the Scientific and Ethics Review Board in College of Medicine, Al-Mustansiriya University. A verbal informed consent was taken from all patient relatives for enrollment in this study.

Study design

This study was a cross-sectional study from single hematological center involved 64 patients with known cases of β-thalassemia major or intermedia that has been treated with blood transfusion and iron chelators. The patients were selected randomly from referrals to the Iraqi Center of Hematological Diseases and Research, regardless of age and gender. Patients with β-thalassemia were divided according to the type of therapy into two groups. Group (A): 34 patients (19 females + 15 males) were treated with blood transfusion plus IV deferoxamine infusion (8 h/day) 30 mg/kg/each 3 days/week. Group (B): 30 patients (18 females + 12 males) were treated with blood transfusion plus oral deferasirox 30 mg/kg/day. Splenectomy had been achieved in 18 patients (10 males + 8 females) and the duration between splenectomy and participation in this study was 2–3 years. Exclusion criteria included patients with sepsis, heart failure, renal failure, active liver disease and rheumatologic diseases.

Hematological parameters

Fasting blood sample 10 mL was taken from an antecubital site from each patient and then centrifuged immediately; sera were stored at −80°C until used.

Serum ferritin in ng/dL was assessed by specific ELISA kit (Human Ferritin ELISA Simple Step ab200018). Serum iron in μg/dL was estimated by specific ELISA kit (serum iron ELISA Kit. ABIN2105464). Serum total iron binding in μg/dL was assessed by specific ELISA kit (MBS2601224 Human Total iron-binding capacity ELISA Kit). All ELISA Kit methods were done according to the manufacturer instructions. Unsaturated iron-binding capacity (UIBC) which measures levels of free transferrin (not bound to iron), UIBC = Total iron-binding capacity (TIBC) (μg/Dl) – serum iron (μg/dL).[16] Complete blood picture was prepared by Automated Touch Screen Hematology Analyzer, Hs Code: 90189090, China (WHY 6480).

Immunological parameters

Serum levels of IgA, IgG, and IgM in mg/dL were assessed by ELISA Kit method (Isotyping kits for human immunoglobulin, fast ELISA, Catalog number RDB3257). Complement levels in mg/dL of C3 and C4 were estimated by complement C4 and C3 Human ELISA Kit (ab108824).

Statistical analysis

Data were expressed as mean ± standard deviation, number and percentage. The unpaired Student's *t*-test was used to evaluate the significance of differences between the treated groups in terms of 95% confidence interval, *t* value with $P < 0.05$ as statistically significant. Data analysis was done using SPSS (IBM SPSS Statistics for Windows, Version 21.0., 2013 Armonk, NY: IBM Corp).

Results

A total number of 64 patients with β-thalassemia aged 16.63 ± 3.94 years, female to male ratio was 1.3:1, most of enrolled patients were white so white:black ratio was 31:1.

Regarding types of thalassemia, it has been found that 67.19% of β-thalassemic patients were major type while 32.81% were intermediate type. The duration of starting blood transfusion was 13.12 ± 2.9 years whereas the duration of starting iron chelation was 4.68% for age <5 years, 60.93% for age 5–10 years and 34.37% for age >10 years.

With respect to iron chelation treatment, 53.12% got deferoxamine and 46.87% got deferasirox. In addition, 18 (28.12%) patients experienced splenectomy. This study pointed that complications recorded in 37.5% of thalassemic

Table 1: Demographic characteristics of thalassemic patients

Characteristics	*n* (%), mean±SD
Age (years)	16.63±3.94
Number	64
Gender	
Male	27 (42.19)
Female	37 (57.81)
Female:male ratio	37:27
Race white:black ratio	62:2
Types of thalassemia	
Major	43 (67.19)
Intermedia	21 (32.81)
Durations of blood transfusion (years)	13.12±2.9
Durations of starting iron chelation (years)	
<5	3 (4.68)
5-10	39 (60.93)
>10	22 (34.37)
Iron chelators	34 (53.12)
Deferoxamine	30 (46.87)
Deferasirox	18 (28.12)
Splenectomy	24 (37.5)
Complications	
Skeletal malformations	8 (12.5)
Recurrent infections	9 (14.06)
Gallstone	2 (3.125)
Hepatitis C	3 (4.68)
Hepatitis B	2 (3.125)

patients which includes recurrent infections 14.06%, skeletal malformations 12.5%, hepatitis C 4.68%, and hepatitis B 3.125% and gallstone 3.125%. The demographic characteristics of thalassemic patients are summarized in Table 1.

In deferoxamine-treated patients, serum ferritin levels were high (8160.33 ± 233.75 ng/dL) compared to deferasirox-treated patients (3000.62 ± 188.23 ng/dL; $P < 0.0001$); also there were significant differences in serum iron, TIBC, and UIBC ($P < 0.0001$) in deferasirox-treated patients compared to deferoxamine-treated patients. There were insignificant differences in hemoglobin and platelet count in deferoxamine and deferasirox-treated patients ($P = 0.7367$ and $P = 0.0721$, respectively) [Table 2].

Indeed, immunological changes between two treated groups (deferoxamine and deferasirox-treated patients) showed insignificant differences in levels of complements (C3 and C4) and immunoglobulin levels (IgM, IgG, and IgA; $P > 0.05$) [Table 3].

Discussion

This study revealed significant effects of deferasirox in reduction of iron overload in β-thalassemia compared to deferoxamine.

In deferasirox-treated patients serum ferritin levels were low compared to deferoxamine-treated patients due to higher efficacy and compliance of deferasirox,[17] since; deferoxamine parenteral administration led to poor compliance and efficacy.[18]

These findings are corresponded with Vichinsky *et al.* study that showed a higher efficacy of deferasirox compared to deferoxamine in the reduction of iron overload in hemolytic anemia.[19] In addition, animal model study demonstrated the effectiveness of deferasirox in the reduction of liver and heart iron overloads more than deferiprone and deferoxamine.[20]

Regarding patients that are treated with deferasirox, both TIBC and UIBC are improved through the reduction of serum iron and iron burden in transfusion-dependent β-thalassemia, since circulating iron is normally bound to transferrin but in a state of iron overload, the capacity for iron binding will be reduced leading to increase in the nontransferrin bound iron. Consequently this will lead to induction of oxidative stress and reduction in the antioxidant capacity, so a high free iron can be taken by cardiac and hepatic parenchyma independent on transferrin receptors causing parenchymal damage.[21]

Moreover, Wood *et al.*'s experimental study demonstrated that deferasirox has cardioprotective and hepatoprotective effects through reduction of intracellular irons; it decreases cardiac iron by 20.5% as deferiprone and both of these drugs are more effective than deferoxamine;[22] these findings are in agreement with our results. Thus, favorable and potential effects of deferasirox were attributed to the long biological half-life which gave a 24 h protection from the effect of iron overload, unlike the deferoxamine effect that gave protection only limited to the time of drug exposure which was about 8 h.[11]

In general, sustained serum ferritin levels >2500 ng/dL are associated with organ toxicity, thus the goal of chelation therapy is lowering serum ferritin below 2500 ng/dL[23] but in this study, serum ferritin level in deferoxamine-treated patients was 8160.33 ± 233.75 due to poor compliance while in deferasirox-treated patients serum ferritin level was 3000.62 ± 188.23 due to unavailability and cost of this drug, but clinically none of our enrolled patients observed signs and symptoms of heart or hepatic dysfunctions in spite of high serum ferritin levels.

Indeed, 12.5% of our patients developed skeletal and growth retardation due to extramedullary erythropoiesis or endocrinopathy as supported by Saffari *et al.*'s study, that revealed a wide range of metabolic and endocrine disorders in β-thalassemia major.[24]

Regarding the immunological changes in deferasirox versus deferoxamine-treated patients, there were insignificant changes in immunoglobulin and complement serum levels, but those levels appear higher in immunoglobulin and low in complement levels compared to the normal reference range.[25]

There is a debate regarding immunoglobulin and complement serum levels in β-thalassemia may be normal, increased IgA only and decreased IgM with significant reduction in complement serum levels.[26]

Higher immunoglobulin and lower complement serum levels in the present study may be due to repeated blood transfusion that leads to uninterrupted antigen exposure which activated immunoglobulin production and complement consumptions, recurrent infections in β-thalassemia also lead to augmentation in immunoglobulin stimulation,[27] also iron burden in β-thalassemia modulates T-helper activity that plays an important role in immunoglobulin activation.[28]

Table 2: The differences between the effect of deferoxamine and deferasirox on hematological parameters of blood transfusion-dependent β-thalassemia major or intermedia

Parameters	Deferoxamine (*n*=34)	Deferasirox (*n*=30)	*t*	95% CI	*P*
Serum ferritin (ng/dL)	8160.33±233.75	3000.62±188.23	97.7179	5054.13-5265.261	<0.0001*
Serum iron (μg/dL)	476.22±72.94	266.39±37.65	14.7008	181.17-238.48	<0.0001*
TIBC (μg/dL)	157.91±44.82	200.55±33.81	−4.3253	−62.35-22.92	<0.0001*
UIBC (μg/dL)	318.31±55.73	65.84±13.39	25.5917	232.48-272.45	<0.0001*
Hemoglobin (g/dL)	10.77±2.37	10.54±2.99	0.3379	−1.133-1.593	0.7367
Platelet count (n/μL)	200004.82±111.7	200056.33±114.88	−1.8304	−108.81-4.816	0.0721

*P<0.01, Data expressed as mean±SD, TIBC: Total iron-binding capacity, UIBC: Unsaturated iron-binding capacity, SD: Standard deviation, CI: Confidence interval

Table 3: The difference between the effects of deferoxamine and deferasirox on immunological parameters of blood transfusion-dependent β-thalassemia major or intermedia

Parameters (mg/dL)	Deferoxamine (*n*=34)	Deferasirox (*n*=30)	*t*	95% CI	*P*
C3	80.5±28.2	82.44±10.37	−0.3735	−12.4158-8.53	0.7106
C4	11.55±4.74	10.76±3.22	0.7875	−1.217-2.797	0.4342
IgM	199.71±27.92	202.63±26.84	−0.4262	−16.61-10.77	0.6715
IgG	1679.63±204.54	1673.72±200.33	0.1164	−95.426-107.22	0.9077
IgA	220.55±44.72	233.51±45.81	−1.1421	−35.65–9.734	0.2579

Data expressed as mean±SD, C: Complement, P>0.05. SD: Standard deviation, CI: Confidence interval

Furthermore, 28.12% of our patients underwent splenectomy which may affect the immunological picture in patients with β-thalassemia since splenectomy leads to the impairment of lymphocyte, macrophage, complement, and immunoglobulin qualitatively and quantitatively.[29] Darzi *et al.* pointed out to the significant reduction in serum levels of both complement (C3) and immunoglobulin (IgA, but not IgM) in β-thalassemic patients after splenectomy.[30] Therefore, splenectomy alters the immune status in patients with β-thalassemia via an unknown mechanism.[31]

Additionally, iron chelators lead to significant humoral immune alterations through induction of anti-histone antibody productions that cause an increase in the immunoglobulin levels in patients with β-thalassemia;[32] Bayraktar *et al.* also revealed the potential role of deferoxamine in enhancement of the response to interferon-alpha response in patients with chronic hepatitis B through an unknown mechanism.[33]

Finally, an observational study done by Aleem *et al.* observed that deferasirox in thalassemic patients led to an increase in the total T and B lymphocytes, CD4, CD8, natural killer cells, and IgG serum levels,[34] which is in concordance with findings of the present study related to the immunoglobulin levels.

Conclusion

This study indicated that deferasirox is more effective than deferoxamine regarding the iron overload but not in the immunological profile in patients with blood transfusion-dependent β-thalassemia.

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Conflicts of interest

There are no conflicts of interest.

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