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Deferasirox Efficacy and Safety in Pediatric Beta Thalassemia Major: A Focus on Liver and Renal Function

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Abstract:

Background: Thalassemia, inherited autosomal recessive disorders, result in reduced or absent globin chain synthesis, causing abnormal hemoglobin and anemia. Chelation therapy and transfusions improve patient lifespan.

Objectives: This study evaluated the 3-year efficacy of deferasirox (Exjade) in transfusion-dependent β-thalassemia and assessed changes in liver enzymes, renal function, and serum calcium.

Patients and Methods: A retrospective comparative study of 50 β-thalassemia major patients (5-17 years) with baseline serum ferritin >1000 ng/ml was conducted. Baseline and follow-up (8-12 weeks) serum ferritin, S.GPT, S.GOT, creatinine, BUN, and calcium levels were analyzed.

Results: Significant serum ferritin reduction was observed, from 3737.88 ng/ml at baseline to 2301.78 ng/ml at 36 months ($p<0.05$). The mean Exjade dose decreased from 36.41 to 33.03 mg/kg/day ($p<0.05$). S.GPT and S.GOT increased slightly in the third year, within acceptable limits, while bilirubin decreased ($p<0.05$). Creatinine showed non-significant fluctuations, but BUN changed significantly ($p<0.05$). Serum calcium showed a mild initial increase, then decreased ($p<0.05$).

Conclusions: Deferasirox significantly reduces serum ferritin in β-thalassemia major patients at doses ≥30 mg/kg. It has milder liver enzyme effects than deferoxamine, though slight increases occur. Renal hemodynamic effects were mild and reversible over 3 years, with no progressive decline.

Key points: Beta-Thalassemia Major, Deferasirox, Iron Chelation Therapy, Serum Ferritin, Liver Function Tests, Renal Function Tests, Long-Term Efficacy, Drug Safety.

THALASSEMIA

Beta thalassemia syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In individuals with β-thalassemia, there is either a complete or a partial absence of β-globin gene production. [1]

In 1932 Whipple and Bradford coined the term thalassemia from the Greek word Thalassa, which means the sea (Mediterranean) to describe this entity. Somewhat later, a mild microcytic anemia was described in families of Cooley anemia patients, and it was soon realized that this disorder was caused by heterozygous inheritance of abnormal genes that, when homozygous, produced severe Cooley anemia. [2]

PATHOPHYSIOLOGY

Two major features contribute to the pathogenesis of sequelae of β-thalassemia: inadequate β-globin chain production, leading to decreased levels of normal hemoglobin (Hb A), and an imbalance in α- and β-globin chain production. [3] In bone marrow, thalassemia mutations disrupt the maturation of red blood cells, resulting in ineffective erythropoiesis; the marrow is hyperactive, but the patient has relatively few reticulocytes and severe anemia. [4, 5]

In β-thalassemia, there is an excess of α-globin chains relative to β- and γ-globin chains; α-globin tetramers (α_4) are formed, and these inclusions interact with the red cell membrane and shorten red cell survival, leading to anemia and increased erythroid production. The γ-globin chains are produced in increased amounts, leading to an elevated Hb F ($\alpha_2\gamma_2$).The δ-globin chains are also produced in increased amounts, leading to an elevated Hb A_2 ($\alpha_2\delta_2$) in β-thalassemia. [5, 6]

THALASSEMIA MAJOR Clinical Manifestations

The classic findings in children with severe thalassemia, including typical facies (maxillary hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia, are primarily seen in developing countries. The spleen may become so enlarged that it causes mechanical discomfort and secondary hypersplenism.

Features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull) and extramedullary hematopoiesis. [6, 7]

Pallor, hemosiderosis, and jaundice may combine to produce a greenish brown complexion. As a result of the anemia, there is also an increase in iron absorption from the gastrointestinal tract, with toxicity leading to further complications. [6, 7]

If not treated, children with β-thalassemia usually become symptomatic as a result of progressive hemolytic anemia, with profound weakness.

Depending on the mutation and the degree of fetal hemoglobin production, transfusions in patients with thalassemia major are necessary in the 2^{nd} 6 months of life or the 2nd year, but rarely later. **6)**

Many of these features became less severe and less frequent with transfusion therapy, but the creation of excessive iron stores associated with hemosiderosis is a major concern in individuals with β- thalassemia. [3, 6]

LABORATORY FINDINGS

Patients with β-thalassemia have severe anemia as the hemoglobin level falls progressively to < 5.0 g/dL unless transfusions are given. The reticulocyte count is inappropriately low compared with the degree of anemia because of ineffective erythropoiesis.

The unconjugated serum bilirubin level is usually elevated. The platelet count is normal or increased but may be low if the spleen is enlarged. After splenectomy, thrombocytosis and increased numbers of nucleated RBC are seen. [3, 6]

Even if the patient is untransfused, eventually there is iron accumulation, with an elevated serum ferritin level and saturation of transferrin. Bone marrow hyperplasia can be seen on radiographs. [2, 6]

The hemoglobin electrophoretic pattern is predominantly HbF. Hemoglobin A is absent in homozygous thalassemia and is present but in small proportions in homozygous or doubly heterozygous thalassemia. Hemoglobin A_2 levels are of little diagnostic value. [6]

IRON OVER LOAD

Occurs when iron intake is increased over a sustained period of time either as result of red blood cell transfusion (100-200 m1 of pure RBC /kg / year), are transfused which is equivalent to 116-232 mg of iron /kg/year or increase absorption of iron through gastrointestinal tract.

In thalassemia patient who do not received any transfusion, iron absorption increase several folds reached to 3-5mg/day. [8] Monitoring of iron over load

Monitoring closely and accurately as possible, iron over load is essential in establishing effective iron chelation regimen. [5]

SERUM FERRITIN

Is relatively easy test, well established, generally correlate with body iron store and prognostically relevant in thalassemia major.

Serum Ferritin is not always reliable for evaluating iron burden because it is influenced by other factors like liver damage, active infection and active inflammation may falsely increase serum ferritin, while vit.c deficiency may depress it. **(3, 5, 9)**

LIVER IRON CONCENTRATION (LIC)

Is now regarded as standard for estimating body iron loading and has been shown accurately to predict total body iron stores**.** Normal LIC values are up to 1.8 mg/g dry weight, with level of up to 7 mg/gm dry weight seen in some nonthalassemia population without apparent adverse effect. [5, 6]

Measurement of LIC can be done by chemical determination on a liver biopsy, quantitative liver iron by approved MRI technology, SQUID (super conducting quantum interference device). [5, 10]

MECHANISM OF IRON TOXICITY

The toxicity of iron is mediate by its catalysis of reaction which generate harmful free hydroxyl radicals propagators related damage which induce lipid peroxidation of cell organelles, causing cell death and generation of fibrosis. [13, 15] Iron is kept safe by binding to molecules such as transferrin but in iron over load, their capacity to bind iron is exceeded both within cells and in the plasma compartment, resulting free iron damages many tissues in the body and is fatal unless treated by iron chelation therapy [11].

TREATMENT

Before chronic transfusions are initiated, the diagnosis of β0-thalassemia should be confirmed and the parents counseled about this lifelong therapy. Initiating transfusion and chelation therapy can be difficult for parents to face early in their child's life. [6]

BLOOD TRANSFUSION

Before transfusion therapy is begun, a red cell phenotype is obtained; blood products that are leukoreduced and phenotypically matched for the Rh and Kell antigens are required for transfusion. If there is the possibility of a bone marrow transplant, the blood should be negative for cytomegalovirus and irradiated. Transfusion therapy promotes general health and well-being and avoids the consequences of ineffective erythropoiesis. In patients with cardiac disease, higher pretransfusion hemoglobin levels may be beneficial. [2, 6]

IRON CHELATION:

Deferoxamine(Desferal)

Deferoxamine is given subcutaneously over 10–12 hrs., 5–6 days a week at a dose of 20-40 mg/kg/day [12].

Approximately 8 mg of iron is bound by 100 mg of deferoxamine. Side effects include ototoxicity with high-frequency hearing loss, retinal changes, and bone dysplasia with truncal shortening, local irritation at injection sites and febrile reaction. The most feared side effect is infection with Yersinia enterocolitica and severe mucomycosis, the number of hours deferoxamine is used daily is more important than the daily dose. High-dose, short-term infusions increase toxicity with little efficacy. [6, 8, 13]

Plasma non-transferrin-bound iron (NTBI) is most likely responsible for the serious iron injury. When deferoxamine is infusing, it binds NTBI. When deferoxamine is stopped, there are rebound increases in NTBI levels, with a risk of injury. [6, 13]

The 24 hrs. deferoxamine infusion has been shown to reverse cardiomyopathy in patients with excessive iron stores in the heart that result in symptomatic congestive heart failure. [6, 8]

Deferasirox (Exjade)

Deferasirox is an orally active chelator that is highly selective for iron, promotes excretion of iron in the faces. Deferasirox also has a lower affinity for aluminum and a much lower affinity for zinc and copper. The recommended initial dose of Ex jade is 20 mg/kg bodyweight once daily taken on an empty stomach at least 30 minutes before food at the same time each day, absorbed following oral administration with a median time to peak plasma concentration of about 1.5 to 4 hours. [14, 15]

Deferasirox is highly (99%) bound to plasma proteins, almost exclusively to serum albumin. Glucuronidation, with subsequent biliary excretion, is the main metabolic pathway for deferasirox. Deconjugation of glucuronides in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. [8]

Deferasirox and its metabolites are primarily excreted in the feces (84% of the dose). Renal excretion of deferasirox and its metabolites is minimal (8% of the dose, 6% as hydroxylated deferasirox). The terminal elimination half-life ranges from 8 to 16 hours. [13, 16]

Liver function should be monitored every month and should be discontinued if there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes. [17]

Development of deferasirox

Deferasirox (Exjade®, ICL670) was developed in response to the clear need for a convenient, effective and well-tolerated iron chelating agent. The development process began in 1993, when Novartis (Basel, Switzerland) produced over 700 iron chelating compounds with high affinity and selectivity for iron. Using a computational chemistry-based model, the bis-hydroxyphenyl-triazole class showed the most promise, as it combined the relevant iron chelating attributes with the potential to synthesize various derivatives. Approximately 40 compounds with this structure were synthesized. Just one molecule, known as ‘ICL670’ or deferasirox, passed this test and subsequently entered a rigorous clinical development program in 1998.

Deferasirox: properties and administration

Deferasirox is a tridentate iron chelator, meaning that two molecules are required to form a stable complex with each iron (Fe^{3+}) atom. The active molecule (ICL670) is highly lipophilic and 99% protein-bound. The key chelation properties of deferasirox are:

- ✓ High and specific affinity for Fe3+ (approximately 14 and 21 times greater than its affinity for copper [Cu2+] and zinc [Zn2+], respectively [18]
- ✓ Oral bioavailability
- ✓ Highly efficient and efficacious
- ✓ Effective at multiple doses; allowing flexible regimens
- ✓ Long half-life (8–16 hours); allowing once-daily dosing
- ✓ Generally, well tolerated
- ✓ The long half-life means that deferasirox can be taken once a day (standard dose of 20–30 mg/kg/day).

Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained; this oral formulation means that deferasirox is easy-to-use for pediatric

patients. Any residue should be resuspended in a small volume of liquid and swallowed to avoid introducing variability in bioavailability. For the same reason, deferasirox should be taken on an empty stomach at least 30 minutes before food. [19]

Safety and tolerability profile

Deferasirox has been shown to be generally well tolerated in adults and children with different chronic anemias. Of 652 patients who received deferasirox in the core clinical trials, none experienced drug-related neutropenia or agranulocytosis, which were serious adverse events (AEs), observed during treatment with other chelators. [20, 21]

Sporadic cases were observed, but were considered by the investigators to be due to the underlying condition rather than deferasirox therapy.

The most frequent AEs reported during chronic treatment with deferasirox include transient mild-to-moderate gastrointestinal disturbances (~26% of patients) and transient mild-to-moderate skin rash (~7% of patients).

These events rarely required drug discontinuation and many resolved spontaneously. Mild, non-progressive increases in serum creatinine (generally within upper limit of normal [ULN]) were observed in 34% of patients, although these are not currently thought to be clinically significant as they were temporary and reversible. There were no cases of moderate to severe renal insufficiency or renal failure and no patients permanently discontinued therapy due to creatinine rises in the core, 1-year studies. Increases above the ULN were observed in 2% of patients with β-thalassemia major and 16% with other anemias, including geriatric patients whose baseline creatinine levels were close to the ULN.

Deferasirox is also generally well tolerated in children as young as 2 years of age, with a safety profile similar to that observed in adults. [20]

To date, sexual and physical developments have proceeded normally during treatment with deferasirox.

Deferiprone

Deferiprone is a new iron chelator approved by the U.S. Food and Drug Administration for children >2 years of age.

Deferiprone may not be as effective as deferoxamine in total body iron chelation, but may be more effective in removing cardiac iron. [6]

Rapidly absorbed when ingested orally and when given in two or three doses daily, it causes iron excretion lesser than that caused by an equivalent daily dose of deferoxamine over 8-12 hours. A dose of 75mg/kg divided into three sub doses, each given one hour before food is usually satisfactory. [13]

Adverse effects of deferiprone include agranulocytosis, arthropathy which necessitates discontinuation of the therapy. Gastrointestinal intolerance, zinc deficiency and fluctuation of liver enzymes are other side effects. [22]

SPLENECTOMY

Splenectomy is usually not needed if regular transfusion is followed but it is indicated when there is:

- Presence of leucopenia or thrombocytopenia. [23, 24]
- Palpable spleen more than 6 cm bellow left costal margin with hypersplenism. [23, 24]
- Annual blood requirement of 1.5 times or more than that of patient who had splenectomy provided that they are on the same transfusion scheme. [23, 24]

BONE MARROW TRANSPLANTATION

Bone marrow transplantation has cured >1,000 patients who have thalassemia major. Most success has been in children younger than 15 year of age without excessive iron stores and hepatomegaly who have HLA-matched siblings. [6]

All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation in which substitution normal stem cells for stem cells harboring defective globin genes. [6]

GENE THERAPY

Since, thalassemia is characterized by defective synthesis of globin subunits caused by mutations affecting gene regulation or expression, gene therapy remains the ultimate treatment for providing a lifelong cure. In this mode of therapy, patient's bone marrow is harvested and beta globin gene is incorporated into stem cell and re-infused in the body system [9, 25].

COMPLICATIONS OF THALASSEMIA

Many of the complications of thalassemia seen today are the result of increased iron deposition from repeated blood transfusions. Complications can be avoided by the consistent use of an iron chelator. However, chelation therapy also has associated complications. [6]

1. People with thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver and endocrine system, which includes glands that produce hormones that regulate processes throughout the body. Without adequate iron chelation therapy, almost all patients with beta-thalassemia will accumulate potentially fatal iron levels. [26]
2. **Infection:** people with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed. [27]
3. **Bone deformities:** Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones. [6, 27]
4. the spleen aids in fighting infection and filters unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of a large number of red blood cells, and the task of removing these cells causes the spleen to enlarge. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may necessitate its removal. [27]
5. **Endocrine dysfunction:** may include hypothyroidism, gonadal failure, hypoparathyroidism, diabetes mellitus, growth hormone deficiency, osteoporosis, and delay puberty. [2, 6, 27]
6. **Heart problems:** Congestive heart failure and cardiac arrhythmias are potentially lethal complications of iron stores in individuals with thalassemia. [27]

IRON METABOLISMP Histological Roles For Iron

Iron not only transports and stores oxygen, it has several others function, outside the red blood cell. These functions include:

- ✓ Carrying electrons and acting as a catalyst for oxidative metabolism.
- ✓ Playing a role in synthesis of DNA, and cellular growth and proliferation in many body tissues.
- ✓ Participating in neurotransmitter synthesis and function.
- ✓ Contributing to the process in which certain specialized cells called phagocytes detect, ingest, and kill bacteria.

- ✓ Playing a role in the detoxification of chemicals and poisons in the liver. [8]

IRON ABSORPTION

The primary mechanism for getting iron into the body is through dietary ingestion. Iron is absorbed in the proximal small intestine, mostly in the duodenum, but also in the upper jejunum. [28]

Arrival in the Bone Marrow

Once absorbed into the blood, iron is bound to circulating transferrin, which carries it initially through the portal system of the liver, the major site of iron storage.

Here hepatocytes take up some of them but eventually most of it reaches the major site of iron utilization, the bone marrow, where it is used in the synthesis of the heme portion of hemoglobin. The RBC develops inside the marrow until it becomes a functioning mature RBC circulating in the blood. [28]

Iron Distribution and Regulation

Once iron has been absorbed, there are three possible destinations for it in the body as it may become metabolic iron, storage iron, or transport iron. Hypoxia stimulates erythroid activity. In addition, it may also increase iron absorption independent of the erythropoietic changes regardless of the type of stimulus or the circumstances responsible for increased iron absorption, a maximum of about 3.5 mg iron per day may be absorbed from the diet . [28, 29]

Iron Transport

Under normal circumstances, iron circulating in the plasma is always bound to transferrin because it cannot exist as a free ion in the blood. The liver synthesizes transferrin and secretes it into the plasma. Each transferrin molecule can carry two iron ions. [29, 30]

Iron Storage by Ferritin

The two primary functions of ferritin are:

1. To act as the repository of storage iron in the liver (and other organs).
2. To release stored iron back to transferrin, so it can be recycled into circulating RBCs.

The quantity of iron in storage (about 1,000 mg of iron in the liver plus additional smaller stores in the spleen and intestinal wall) is substantially larger than the quantity of iron being carried by plasma transferrin (about 3 mg). [28, 30]

HEMOSIDERIN

Is an insoluble complex of ferric hydroxide and protein debris comprised of partially or fully digested ferritin, which is derived from excess ferritin in iron loaded cells.

This type of iron is not toxic; however, it is likely that the large volume of the debris has a negative effect on the ability of the cell to function, and may contribute to cell death in iron-overload conditions. [30, 31]

LIVER FUNCTION TEST

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase, bilirubin, and alkaline phosphatase levels, as well as determinations of prothrombin time. These tests are complementary, provide an estimation of synthetic and excretory functions, and may suggest the nature of the disturbance (inflammation or cholestasis). [2]

Acute liver cell injury (parenchymal disease) in viral hepatitis, drug or toxin induced liver disease, shock, hypoxemia, or metabolic disease is best reflected by marked increases in serum aminotransferase levels. [6]

A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatocellular disease or hepatic excretory dysfunction, whereas elevations in aminotransferase levels are more highly sensitive indices of hepatocellular damage. [6]

S.GPT (serum glutamate pyruvate transaminase) is liver specific, whereas S.GOT (serum glutamic-oxaloacetic transaminase) is derived from other organs in addition to the liver. [2, 6]

RENAL FUNCTION TESTS

Serum creatinine and urea concentrations change inversely with changes in GFR and are therefore useful in gauging the degree of renal dysfunction.

Changes in serum creatinine concentration more reliably reflect changes in GFR than do changes in serum urea concentrations. Creatinine is formed spontaneously at a constant rate from creatine, and blood concentrations depend almost solely upon GFR. Urea formation is influenced by a number of factors such as liver function, protein intake and rate of protein catabolism. [32]

Aims of the study

To evaluate the long-term efficacy of deferasirox in patients with transfusion-dependent β-thalassemia and to assess the changes in liver enzymes, renal function and serum calcium after 3 years intake of oral chelating agent deferasirox.

Patients and Methods:

A retrospective comparative analytic study design was done on group of 50 patients (21 patients were males and 29 patients were females) with beta thalassemia major .

Diagnosed by hemoglobin electrophoresis registered in thalassemia center in Karbala pediatric Teaching Hospital in Karbala city, during a period from the 1st of September 2015 through the 1st of January 2016.

Inclusion Criteria:

- ✓ Patients age between 5year to 17 years old
- ✓ No gender limitation
- ✓ Patients diagnosed to have major beta thalassemia
- ✓ Ferritin level above 1000 mg/dl or if the patient had more than 10 times of blood transfusion
- ✓ Normal serum creatinine level
- ✓ No proteinuria in urine analysis
- ✓ Negative serologic tests for HCV, HBV and HIV
- ✓ Liver transaminases below 5-fold the normal upper limit

This information was taken from card visit that is found in the thalassemia center.

Any patient with data or information against the mentioned above did not included in this study.

Data collection

Data were collected from the patient's cards, include:

Name, age, sex, weight, age of first blood transfusion, frequency of blood transfusion per year, age of starting chelating agent, date of starting Exjade, dose of Exjade, and previous surgical history including splenectomy.

The information's were taken from the card visit as each patient has his/her own card visit that contain information's mentioned above in addition to the previous and recent investigation regarding (S.F, Hepatic, Renal, Cardiac function) and even auditory and ophthalmological

investigation as these problems are common in Thalassemic patients, according to the inclusions criteria 50 patients included, all the patients (100%) were treated with Exjade.

INVESTIGATIONS

Following parents' consent, blood is drawn from a vein by a needle with syringe after antiseptic technique. Blood samples (4cc) were taken for evaluating (S.ferritin, LFT, RFT, S.Calcium).

1. S.ferritin

Material was used ' ACC U-BIND ELIZA MICROWELLS.

Morning blood samples were collected in a plain red venipuncture tube without additives or anticoagulant. Blood then allowed clotting for centrifugation to separate the serum. The value is expressed in ng/ml.

2. Liver functions: which include S.GOT, S.GPT and TSB.

Regarding patients on Exjade, tablets were advised to be dispersed in a non-metallic glass of water (apple or orange juice if patient could not tolerate) until a fine suspension was obtained and it was taken on an empty stomach 30 min before a meal preferable at the same time each day, while patients on Desferal were informed about using the drug in correct way by using subcutaneous infusing pump preferable at night for 10-12 hours per day for at least 5 days per week and that the number of hours Desferal used daily is important as high-dose, short-term infusions increase toxicity with little efficacy.

Mean Baseline LFT were taken prior to the start of treatment and then were assessed every 8-12 weeks.

According to wide alternation in serum ferritin level in different clinical situations, in this study primary efficacy end-point was the mean of 3 months changes in serum ferritin concentration during 1^{st} year, 2^{nd} year and the 3^{rd} year of treatment compared with baseline.

Mean baseline S.ferritin was taken for patients on Exjade therapy and then followed every 3 months to determine the percentage of decrement every 3 months and all over the 3 years of treatment.

For patient on Exjade Mean baseline serum ferritin was 3737.88 ng/ml. According to the serum ferritin level dose adjustment might become necessary.

Dose increases in steps of 5–10 mg/kg monthly for those didn't show a downward trend. During the study, doses above 30 mg/kg /day were allowed.

Variable ranges of liver enzymes level were before starting Exjade treatment as following; (the mean of SGPT was 21.11, the mean of SGOT was 15.25 and the mean of TSB was 1.28).

Monthly visits (for patients with liver enzymes level equal or above 3 folds) and bimonthly or at least trimonthly laboratory follow up profile were requested during the study for the rest of the patients.

Increase serum transaminase level more than 4 folds above the normal was considered as severe liver dysfunction and indicated transient or permanent discontinuation of the drug.

STATISTICAL ANALYSES

1. The data management and analysis were performed by using the statistical package for social sciences (SPSS) program version 21, US, 2014.
2. Descriptive statistics were presented as mean, standard deviation, frequencies (numbers) and proportion (%).
3. Student's t test was used to compare more than two means. While analysis of variances (ANOVA) test was used to compare more than two means. P-values less than 0.05 were

considered as statistically significant; finally, the results and findings of current study were presented in tables and or figures with an explanation of each.

RESULTS

3.1: Distribution of Thalassemic Patients by Age and Sex

The overall mean age of Thalassemic patients was (10.34±3.40) years old and (54.0%) of patients were older than 10 years (Figure 3.1). (58.0%) of Thalassemic patients were females (Figure 3.2).

3.2: Distribution of Thalassemic Patients by Frequency of Blood Transfusion

The overall mean of blood transfusion along years for Thalassemic patients was (50.44±12.26). Figure 3.3 shows the distribution of Thalassemic patients by Frequency of Blood Transfusion. (54.0%) of Thalassemic patients had blood transfusion less than 50 times along years.

3.3: The decrement in serum ferritin along years

Figure 3:4 shows the decrement in serum ferritin from the baseline level through the three years of treatment with deferasirox.

3.4: Mean Differences of Thalassemic Patients Parameters along Years

Table 3.1 shows the mean differences of Thalassemic patients' parameters along years. There were significant mean differences of S.ferritin, S.GPT, S.GOT, TSB, B.urea, S.creatinine and S. calcium along years.

3.4: Mean Difference of Exjade Therapy along Years

Table 3.2 shows the mean difference of Exjade therapy along years. There was significant mean difference of Exjade therapy along years.

DISCUSSION

With widening therapeutic and investigative/monitoring options in iron chelation therapy, an emerging theme includes the benefits and safety of the chelating agent.

Three years of deferasirox treatment led to a sustained reduction in iron burden in most of our patients. In this study, we enrolled patients with transfusion-dependent β-thalassemia whose serum ferritin levels were ≥1000 ng/mL to receive deferasirox.

The initial dose regimens in a number of earlier studies were conservative, so the starting dose in this study was higher based on the experience of several investigators that the response of serum ferritin was indeed dose dependent and a minimum dose of 30 mg/kg was needed to achieve a negative iron balance. [20]

Cappellini et al. [20] showed in their cohort that at doses of 5-10 mg/kg, the iron stores actually increased while at 20 mg/kg, it was possible to achieve neutral iron balance. However, to achieve a negative iron balance, a minimum of 30 mg/kg was required. Taher et al. [9] also documented this in the seminal escalator study. The safety of deferasirox at doses ≥30 mg/kg has been well documented by Taher et al. [33] The study clearly documented improved iron clearance at doses up to 40 mg/kg/day without any increase in the incidence of adverse events.

The mean starting deferasirox dose used in the study was 36.41 mg/kg/day, which was based on the premise that a dose of 30 mg/kg/day was required to actively reduce the iron load. The dose was escalated to 40 mg/kg/day in steps of 5 mg/kg/day if there was inadequate response and according to the patient's complaisance.

At the end of 36 months the mean dose was 33.03mg/kg, which was statistically significant results, p- value <**0.049**, (Table 3.2).

Our study revealed that patients on Exjade treatment show significant decline in SF ,(P-value<0.001), as mean baseline serum ferritin was 3737.88 ng/ml and after 3years of treatment

mean serum ferritin level was 2301.78 ng/ml, this result can be explained by that; serum ferritin is a marker of iron overload but also an acute phase reactant protein. Reduction in serum ferritin may reflect a beneficial effect of Deferasirox on reducing iron overload, beside possible anti-inflammatory effect of Deferasirox or both phenomena [34].

This result similar to the study done in Greece [35], that show Deferasirox produced a significant reduction of mean serum ferritin levels after 12 months of treatment from 1,989±923 to 1,008±776 ng/ml, (P<0.001), but there is more rate of decrement approximately 50% of the mean values. Another study, Ali Taher [33], show that Deferasirox at doses of >30 mg/kg/day significantly reduced serum ferritin to below the levels prior to dose escalation by 487 ng/ml, (P < 0.0001). Mean of Relative Changes of serum ferritin was14.2%.

Another study done in Iran [36], showed significant decline in SF during one year of iron chelating therapy with Exjade, (P value<0.001). Mean of relative changes of serum ferritin was 38.9±11.4 %.

Regarding LFT changes (SGPT, SGOT and TSB), patients on Exjade show increment of liver enzymes at the 3rd year of treatment, but does not reach level of more than 5-fold and only lead to transient discontinuation of the drug. Statistically significant results, p- value < o.o5, (Table 3.1). This result can be explained by that, progressive accumulation of storage iron is associated with cellular toxicity, although the specific pathophysiologic mechanism for hepatocytes injury and liver fibrosis are not entirely understood. These include peroxidation of organelle membranes, increased lysosomal fragility and decreased mitochondrial oxidative metabolism but could be also due to side effect of the drug or other factor affecting the liver such as infection or inflammation. [37]. Ali Taher [33], this study shows that, 9 patients (3.4%) had S.GPT levels of >5 ULN (upper limit normal) but < 10 ULN at two consecutive assessments at least 7 day apart, all of whom had S.GPT >ULN prior to escalation to doses >30 mg/kg /day. Three patients, two of whom who had S.GPT < ULN prior to dose escalation, had S.GPT values of >10 ULN at two consecutive visits after escalation.

S.GPT, S.GOT increase during the 3rd year of treatment with more percentage of increment in S.GOT for patients taking Exjade therapy with statistically significant, p- value <0.039, this may be expected due to the fact that Exjade is mainly excreted by liver and the damage to the hepatocytes by increase LIC, facilitate liver cell damage and increase so liver enzymes [6].

This result differ to the study done in Greece [35], that show after 12 months of Deferasirox administration, mean levels of S.GPT and S.GOT reduce by 40% and 30%, respectively.

Another study done in Italy [21], show that most patients had normal S.GOT levels at baseline, though a relevant proportion (32%) S.GPT increased, presumably reflecting liver damage due to chronic viral hepatitis and/or iron overload. No patient developed consistent or progressive elevations in transaminase levels.

Another study done in Japan [38], show all three patients who received Exjade therapy show a decrease in S.GOT level in association with a decrease in S.F level and suggest that Exjade therapy could be considered to improve liver damage for iron-overloaded patients with an abnormal S.GOT level.

Our study reveals that there's decrement in total serum bilirubin at the end of the 3rd year of treatment with Exjade with statistically significant, p- value < 0.001, (Table 3.1).

This can be attributed to the fact that deferasirox therapy reduces hepatocellular inflammation and improve liver functions that may be linked to the reduction in liver iron concentration and serum ferritin [39].

This result differ to the study done in France [40], show fifteen patients (15.3%) developed hepatotoxicity at a median 60 (13–198) days after the administration. The hepatotoxicity was increased AST/ALT >5×ULN in 14 patients, and increased bilirubin >3×ULN in 1 patient.

Regarding RFT changes (S.creatinine, blood urea), our study reveals increment in S.creatinine in the 1st two years and decrement in S.creatinine in the 3rd year of treatment with Exjade, but statistically not significant, pvalue = 0.268, (Table 3.1).

This result similar to the study done in India [41] ,that shows Mild, non- progressive increases in S.creatinine levels were recorded in 53% of the patients but only 11% of these required a temporary discontinuation and none required permanent discontinuation or developed progressive renal dysfunction.

Our study differ to study done in Iran, fifty eight out of 407 (14.2%) cases had a rising creatinine not only greater than 33% of the baseline level but also more than upper limit of normal for age, 55 of them were children (<15 years old) and 3 of them were older than 15 years of age [36].

About blood urea, this study shows that there's increment in the 1st two years followed by decrement in the 3rd year of treatment with Exjade, statistically significant, p-value<0.001, (Table 3.1).

This result differ to other investigators and studies about the effect of Exjade on renal function, Vladislav Smolkin, Raphael Halevy et al. demonstrating No difference in blood urea nitrogen (BUN), serum creatinine, creatinine clearance, electrolytes, fractional excretion of sodium and potassium, and tubular phosphorus reabsorption was found [42].

Regarding the safety of oral chelator deferasirox and its effect on serum creatinine and blood urea was very clear in this study, even with sustained dose of deferasirox (40mg/kg/day) throughout three years period, which is differ to MN et al. [43]

The fluctuation in blood markers of renal function tests, which were described as mild and remained within the normal laboratory range could be explained by that, underlying mechanism for renal dysfunctions inpatients with βTM is not clear. They seem to be multifactorial, attributed mainly to include long-standing anemia, chronic hypoxia and iron overload, anemia can lead to activation of the oxidative stress cascade once again with the end result of lipid peroxidation and cell damage and eventual functional change of the tubules [44].

So the increment in the 1st two years is due to the potential effect of oral chelator (Exjade) as it can potentially lead to consequences on renal function from prerenal effects, as a result of volume depletion from diarrhea and vomiting-related adverse events, to hemodynamic and specific nephrotoxicity.

Therefore, this apparent nephrotoxicity is in part hemodynamic, reversible and may account for some of the cases of acute kidney injury and would appear safe in low risk patients with no underlying renal disease. The mechanism for this change in renal blood flow may in part relate to chelator-induced iron depletion, affecting the afferent arteriole via an upregulation of prostaglandin production and arteriole vasoconstriction [45].

Gattermann et al. reported that a greater velocity of iron removal was associated with elevated serum creatinine levels, and hypothesized that this may be related to hemodynamic modifications [46].

Although deferasirox is able to readily enter cells because of its lipophilicity, it forms a highly charged complex with iron, which one would predict will not readily efflux from cells. This triple negative charge of the deferasirox-iron complex may therefore in part explain the nephrotoxic potential of deferasirox [47].

The decrement in the 3rd year explained by, chelation therapy is an established treatment for heavy metal poisoning. Heavy metals, which cannot be metabolized, physiologically excreted, persist in the body and exert their toxic effects by combining with one or more reactive groups (ligands), essential for normal physiological functions, many chelating agents exist and have been used in the treatment of many metal poisoning disorders and aluminum toxicity in renal failure. Chelators are been used for the treatment of chronic iron overload in patients with thalassemia major.

Beside that deferasirox is primarily metabolized by glucuronidation, with subsequent biliary excretion. Renal excretion is low (∼8%) [9, 17].

Although this study had several limitations, it presents valuable information for the practicing clinician. The study sample size was small; a single center was used and the data was observational. Therefore, one can only assume that any causal relationships are speculative. There was no detailed assessment of potential *de novo* renal disease, which may occur and exacerbate glomerular.

Regarding serum calcium, this study show mild increment in serum calcium after the 1st year, followed by mild decrement in the last two years of the study, which was statistically significant, p-value < 0.001, (Table 3.1).

This result agreed with Grundy et al. reported lower serum levels of calcium and phosphate in children with βTM and contributed their findings to either liver or parathyroid glands involvement. [48]

Conclusions

1. The study results confirm that Exjade significantly reduces serum ferritin in the majority of patients with thalassemia major.

A dose of ≥30 mg/kg is required to achieve a negative iron balance; it appears to be safe and efficacious even in patients with very high iron load.

2. Exjade has less effect on liver enzymes although there is increment of liver enzymes during the study period.
3. Long-term iron chelation therapy was associated with a manageable safety profile and did not significantly affect kidney function in most of patients

Recommendations

1. It is advisable to include other methods for detection of iron overload and assessment of liver tissue iron concentration (SQUID and R2 MRI) in studies as soon as these measures became available in the future.
2. In order to get better assessment of renal function, urinalysis should be done monthly, to assess proteinuria.
3. Conductingthis study on larger sample, and prolong the follow up period.

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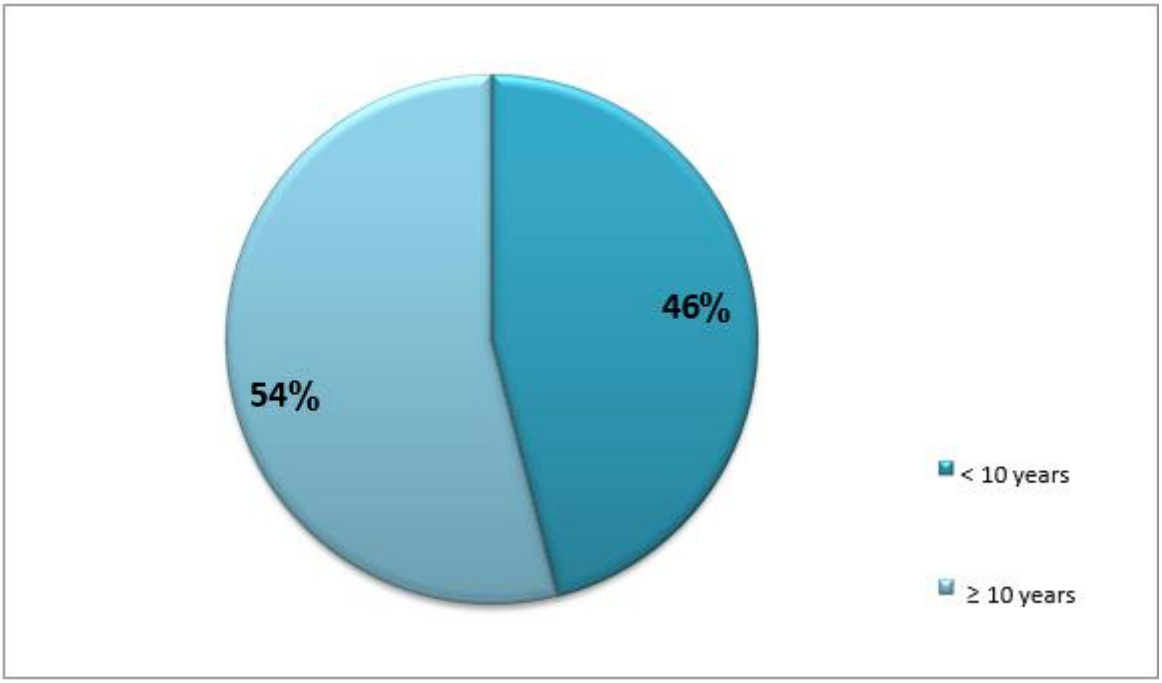

Figure 3.1: Distribution of Thalassemic patients by age groups

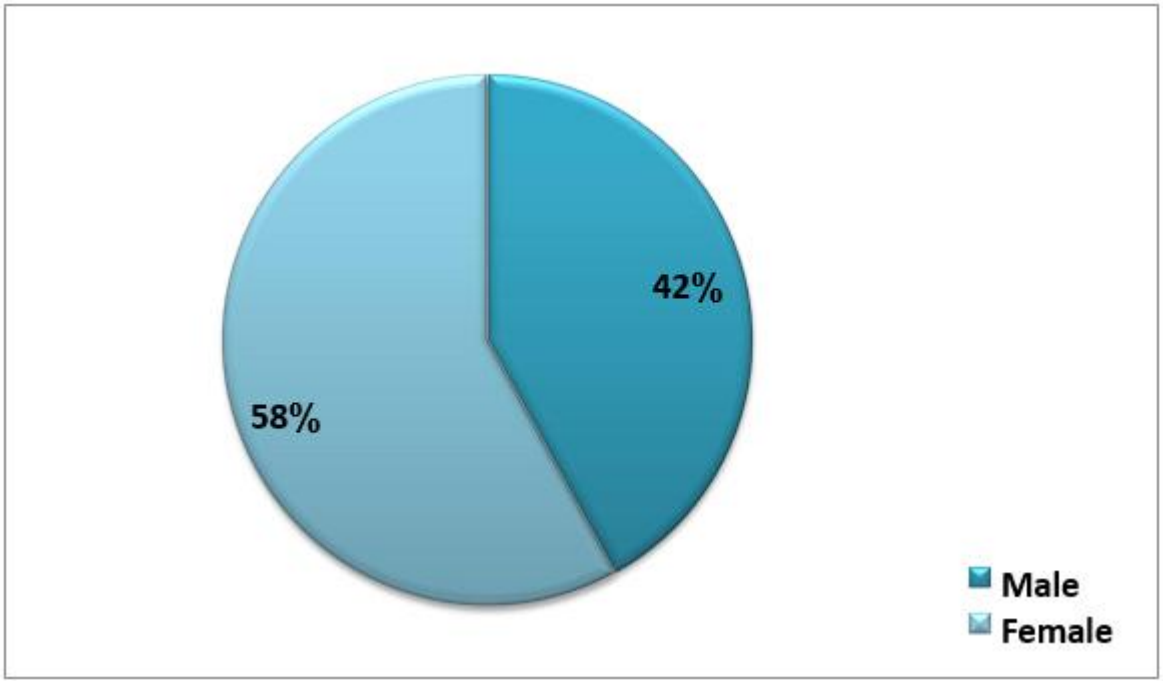

Figure 3.2: Distribution of Thalassemic patients by sex

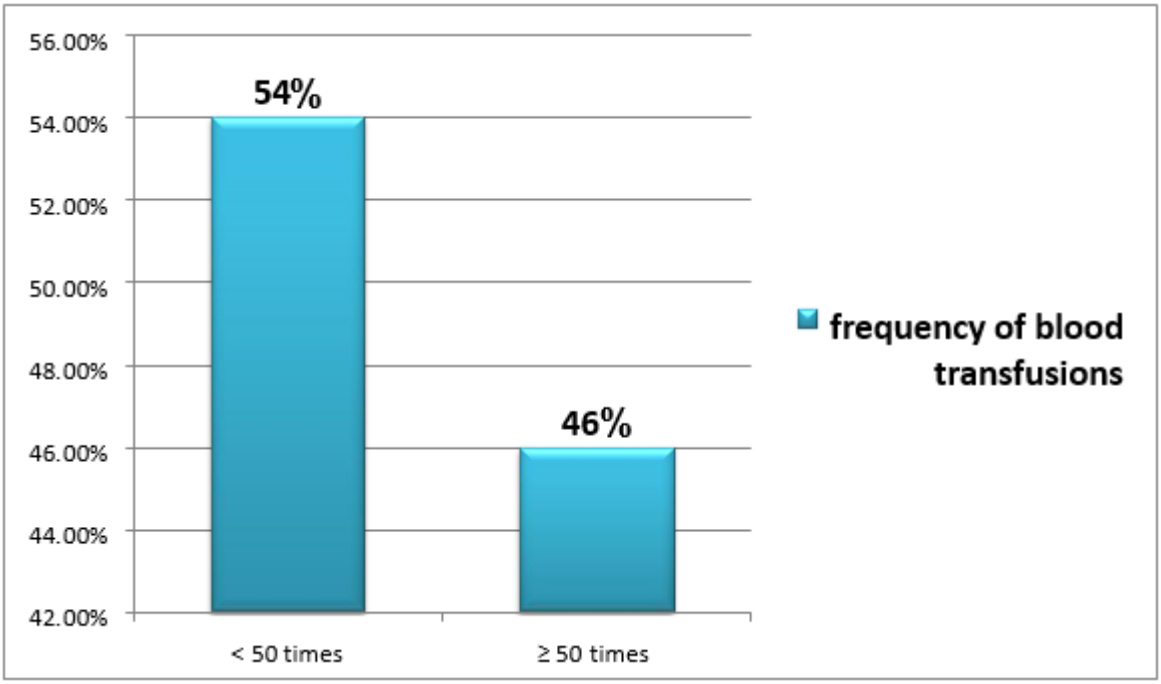

Figure 3.3: Distribution of Thalassemic patients by Frequency of Blood Transfusion

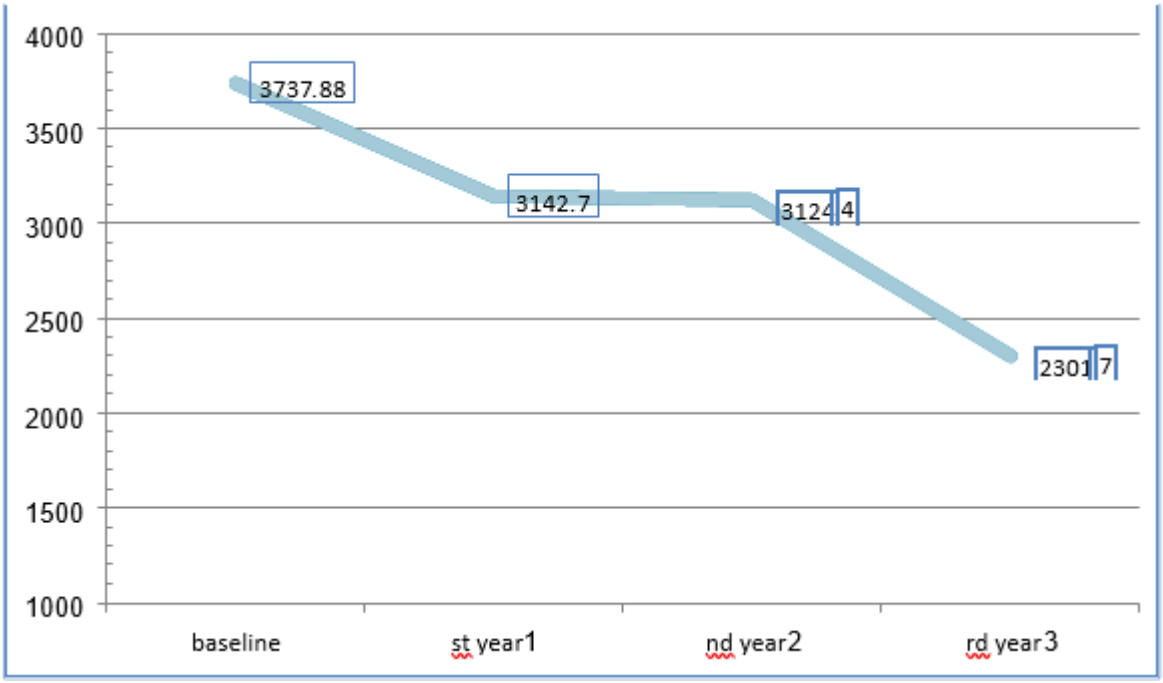

Figure 3.4: Decrement in the mean of serum ferritin

Table 3.1: Mean Differences of Thalassemic Patients Parameters along Years

Parameter	Reading	N	Mean	S.D	ANOVA	P value
S. Ferritin	Baseline	50	3737.88	1633.51	**7.955**	**<0.001***
	1st year	50	3142.70	1593.40		
	2nd year	50	3124.42	1518.58		
	3rd year	50	2301.78	1112.95		
S.GPT (ALT)	Baseline	50	21.11	20.69	1.327	0.267
	1st year	50	17.10	23.31		
	2nd year	50	15.26	9.36		
	3rd year	50	22.20	23.73		

S.GOT (AST)	Baseline	50	15.25	12.83	**2.834**	**0.039***
	1st year	50	15.44	27.67		
	2nd year	50	11.40	7.81		
	3rd year	50	21.34	14.00		
TSB	Baseline	50	1.28	0.66	**6.241**	**<0.001***
	1st year	50	1.33	0.58		
	2nd year	50	1.64	0.60		
	3rd year	50	1.15	0.50		
B.UREA	Baseline	50	29.91	7.87	**16.306**	**<0.001***
	1st year	50	35.06	7.52		
	2nd year	50	33.32	5.68		
	3rd year	50	25.33	8.62		
S.CREATINIE	Baseline	50	1.31	4.71	1.323	0.268
	1st year	50	0.72	0.13		
	2nd year	50	0.69	0.09		
	3rd year	50	0.40	0.20		
S. Calcium	Baseline	50	8.37	0.64	**12.149**	**<0.001***
	1st year	50	8.95	0.67		
	2nd year	50	8.17	0.73		
	3rd year	50	8.12	0.99		

*p value ≤ 0.05 is significant

Table 3.2: Mean Difference of Exjade Therapy along Years

Reading	N	Mean	S.D	ANOVA	P value
1st year	50	36.41	3.23	**2.988**	**0.049***
2nd year	50	35.11	5.78		
3rd year	50	33.03	5.49		

*p value ≤ 0.05 is significant