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Evaluation the Toxicity, Safety, and Efficacy of Deferasirox Locally Manufactured Product in Iron Chelation of Hemoglubinopathic Patients in Iraq

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Abstract

Background: Thalassemia is a genetic condition that requires at least one parent to be a carrier, this condition is inherited. Certain types of blood diseases are characterized by frequent transfusions of blood, including sickle cell disease, anemia, and thalassemia. Blood transfusions offer many advantages, but they might cause the body to store too much iron. Extra iron in the body can lead to serious complications. Eliminating excess iron may reduce the risk of certain disorders. IpJade (deferasirox) is a medication used to treat chronically high iron levels in the body caused by frequent blood transfusions.

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Objective: The aim of the present study is to identify the safety and efficacy of deferasirox locally manufactured product in iron chelation of hemoglubinopathic patients in Iraq.

Patients and Methods: This study was done at the Children's Educational Hospital / Hemoglobinopathy center in Karbala. 100 patients' medical records were acquired randomly who were diagnosed with B-thalassemia Major between the ages of 5 to 27. The information recorded included whether the patient was male or female, the daily dose of Deferasirox prescribed for each patient, and common side effects the patients were experiencing, as well as hepatic and renal function biomarkers.

Results: The results obtained from this study showed slight changes in some biomarkers (WBC, AST, serum ferritin) while clear and strong changes in other (ALT. Alkaline phosphate, serum creatinine) before and after the treatment. The findings of this study revealed a statistically association between the serum creatinine and Deferasirox doses in addition to hepatic enzymes.

Conclusion: This study revealed that the iron chelating agent (Deferasirox) is proven to be the best for patient compliance due to its favored administration compared to other types, it is shown to be well tolerated and efficacious in patients despite some negative effect which need periodic monitoring.

Keywords: Blood transfusion, Derferasirox, Iron overload, Thalassemiam

Introduction

Haemoglobin is a protein composed of iron and changes of alpha and beta globin. It is found in the blood of numerous animals. It is located in the red blood cells of vertebrates, which carry oxygen to the tissues. Hemoglobin forms an unstable, reversible bond with oxygen. It's brilliant red when oxygenated, and purple blue when decreased (1).

Hemoglobin is produced by the bone marrow cells that become red blood cells. When red blood cells are wasted, their hemoglobin is decomposed: iron is saved, it is

transported to the bone marrow by proteins called transferrin, and reused in the creation of new red blood cells; the remainder of the hemoglobin is expelled into the feces, which has a yellow-brown color. This is attributed to the chemical makeup of the feces (2). A tetrahedral organization is composed of four groups of hemoglobin that surround a group of globin in each molecule of hemoglobin. Heme is composed of a complex ring-like structure called a porphyrin that comprises iron atoms, this makes up just 4% of the molecule's weight. As the blood flow between the lungs and the tissues is consistent, the iron atom is attached to oxygen. Every molecule of hemoglobin has four iron atoms, which allows it to attach four molecules of oxygen, and the protein is composed of two connected peptides (3).

Quantitative disorders, such as thalassemia's, is an inherited disorder in which the synthesis of the globin chains that make up haemoglobin is quantitatively reduced (4). This class of illness can be heterozygous, which occurs when one gene is abnormal and the other is normal, or homozygous, which occurs when both genes that code for that feature are abnormal (5). In other instances, however, two separate mutations on the loci of two homologous genes (i.e., double heterozygosity) result in a combined illness. For example, the beta thalassemia gene from one parent and the Hb gene from the other parent might result in beta S beta thalassemia (6)

People from the Mediterranean nation were the first to be described with thalassemia. The condition was frequently observed in areas near the Mediterranean Sea, thus the phrase "thalassa" in Greek, which means "the sea" Traits for thalassemia are more common in people from Mediterranean countries, like Greece and Turkey, and in people from Asia, Africa, and the Middle East (7).

The severity of the disorder varies from mild to severe depending on the number of deletions in each of the four alleles of the alpha globin gene. The most severe variant, four allele deletion, causes no alpha globin production and the synthesis of tetramers from excess gamma chains present throughout fetal development. It is harmful to life

and causes fatal of the fetus. One allele alteration is the most diminutive and least significant variation in medicine (8).

Point mutations in the beta-globin gene cause beta-thalassemia. The primary deficiency in Beta-thalassemia is a decreased or lack of production of Beta globin chains with an excess of alpha chains that are deposited in the bone marrow, this causes the precursor cells to become disabled, this results in the destruction of many red blood cells in the bone marrow and causes damage to the membrane (9). Thalassemia could be divided to major, intermediate, and minor types according to the beginning of symptoms appearance and the severity of the disease, the major types symptoms appear with the second year of baby life or earlier, intermediate type may appear at adulthood while the minor type is considered the lowest form in the severity and the patient may experience slight anaemia or not detected (10).

Iron Overload

Iron overloading is frequent in patients who receive long-term transfusions of blood, the human body lacks the necessary mechanism to expel the excess iron Iron accumulation is detrimental to many tissues, this includes the heart, liver, kidneys, and the brain. These outcomes include the failure of the heart, cirrhosis, growth loss, and multiple endocrine issues. Once iron has been deposited in the tissues, the damage is often irreversible; as a result, chelation therapy should be initiated before the tissue iron has reached a toxic level that will help to reduce the burden of iron and prevent long-term complications associated with iron accumulation in vital organs (11).

Deferasirox

Deferasirox is an iron oxide compound composed of N-substituted hydroxyphenyl groups. This mineral is powerful enough to be taken as a supplement and has a selective effect. The drug was approved by the FDA in 2005 as first-line therapy for

blood transfusions associated with iron overload and in 2006 by the European Medicines Agency (EMA). In March 2002, the EMA classified deferasirox as an "orphan chemical" (12).

The EMA hypothesizes that persons older than 2 years with transfusion-dependent or non-transfusion-dependent iron overload play an important role in the development multiple organ damage. Other forms of anemia (thalassemia) may also be considered. The EMA recommends that treatment should only be started if the patient has high amounts of iron in a chronic state. This is determined by transfusing 100 ml/kg of packed red blood cells (eg 20 units for a 40 kg person).) or a serum ferritin level above 1,000.

Deferasirox (DFX) has been shown to be an effective drug in reducing iron levels in the body and preventing tissue damage. Despite being tolerable, DFX carries significant risks and toxicities that may require temporary cessation of dosing or other supportive treatment (13).

The first daily oral chelated iron, deferasirox (DFX), is a three-bond ligand with high affinity and specificity for iron. The active form of lipophilic agents has a strong preference for proteins, especially albumin. It can be used alone or in combination with deferiprone or deferoxamine, the latter of which are particularly common in iron-related heart disease (14).

The primary method of metabolism of DFX is glucuronidation by uridine diphosphate glucuronosyltransferase (UGT). This results in the production of the metabolites M3 (acylglucuronic acid) and M6 (2-O-glucuronic acid). 6% of the prodrug is metabolized by cytochrome P450 1A1 and 2D6, producing metabolites M1 (5-hydroxy-DFX) and M4 (50-hydroxy-DFX), respectively. Only 8% of DFX and its metabolites are excreted in the urine, but 84% are excreted in the intestines (15).

In humans, DFX is rapidly absorbed and distributed throughout the body with a volume of distribution (Vd) of 14.37-2.69 L and a time to maximum plasma concentration (Tmax) of 1-4 hours after administration. DFX has many indirect effects, including: gastric upset, modest increases in renal blood flow, occasional proteinuria, and hepatotoxicity at higher. A 20% decrease in glomerular filtration rate (GFR) and majority of cases of renal tubular failure leading to electrolyte imbalance have been documented in children (16)

Deferasirox should be taken daily on an empty stomach, at least 30 minutes before meals, and should be taken at the same time each day. Disperse the tablets in water, orange juice, or apple juice to form a thin suspension. Dose distributed in 3.5 oz of fluid and 7 oz of fluid (17).

The highest permitted dose of Deferasirox currently is 30 mg/kg per day in multiple countries. This decreases the serum level of ferritin and the concentration of iron in the liver, and it achieves a negative iron balance. However, some patients need to increase the dosage to greater than 30mg/kg per day in order to achieve their therapeutic goals. This analysis evaluated the effectiveness (as determined by changes in serum ferritin levels) and safety of deferasirox-30 mg/kg per day in patients of both sexes with anemia that was dependent on transfusions, including β-thalassemia, sickle cell disease, and the myelomas plastic syndromes (18)

There was no increase in the severity of renal or liver issues following the escalation of doses. Deferasirox-30 mg/kg/per reduced the iron load to a level that was less than the prior dose increases in patients with dependent anemia on transfusions. Deferasirox has multiple interactions with drugs like aspirin, Aluminum salts, CYP, and other multiple-drug interactions (16).

Study Design and Setting

In terms of the procedure, this study was carried out from the data of patients from the Children's Educational Hospital from the hemoglobinopathy center in Kerbala province/ Iraq from July 2022 to December 2022. Medical records were acquired of 100 patient's that were randomly selected who were diagnosed with B-thalassemia Major between the ages of 5 to 27 years. The following biomarkers were recorded for each patient in addition to the sex, age, dose.

Serum Ferritin, Blood Urea Nitrogen, Serum Creatine, Alkaline Phosphate, Alanine Transaminase, Aspartate Aminotransferase.

White Blood Cell count.

Statistical Analysis

The collected data of the present study were entered from the data analysis sheets and analyzed through the statistical package for the social science (SPSS version 26). Statistical association was considered significant when p value equal or less than 0.05 (p value ≤ 0.05).

Ethical Consideration

Approval of the study protocol was obtained from the Scientific and Ethics Approval Committee of the College of Pharmacy/ University of Kerbala November 3, 2023.

Results

The laboratory evaluation of biomarkers is a critical component of the diagnostic and monitoring process in many medical conditions, including thalassemia. The assessment of various biomarkers helps clinicians to detect and evaluate the severity of a disease, monitor the efficacy of therapy, and detect potential side effects. In thalassemia, several biomarkers are commonly used to monitor the effectiveness and safety of chelation therapy.

Demographic Description of Patients:

Table 1: Age and Gender categories of patients

Characteristic		Total 100
Age in years	Range	5-27
	Mean± SD	16± 5.2
Age in groups	5-12	50
	13-20	32
	21-27	18
Gender	male	49
	female	51

This table describes the demographic of the patient population that was included in the research.

Table 2: Mean Basal vs After Rx parameter comparison of biomarkers included in this study

parameter		mean± SD	P value
Serum ferritin	Basal	3052.6±2303.6	0.116
	After Rx	2769.07±1996.1	
Blood urea	Basal	22.9±10.1	0.007*
	After Rx	27.0±8.6	
Serum creatinine	Basal	0.41±0.15	0.0001*
	After Rx	0.64±0.31	
ALP	Basal	151.5±75.5	0.0001*
	After Rx	202.7±109.1	
ALT	Basal	22.2±11.5	0.0001*
	After Rx	33.8±27.7	
AST	Basal	36.1±16.6	0.53
	After Rx	38.2±31.2	
WBC	Basal	9.2±3.2	0.11
	After Rx	11.5±13.9	

ALP: Alkaline phosphatase, ALT: Alanine Transaminase, AST: Aspartate Transaminase, WBC: White Blood Cells, RX: after treatment. *: Significant, P value is considered ≤0.005.

Table 2 describes the mean of the biomarkers that were recorded and how much deviation from the mean. Subject biomarkers were taken at baseline (before any treatment) and as well as after treatment with Deferasirox.

Table 3 explain the mean differences and stander error of blood urea, ALP, and white blood cells between different age groups.

Table 3: Age category differences between parameters

Parameter	Age category	Mean difference	SE	P value
Blood urea	5-12	9.95	3.47	0.007
	13-20			
Alkaline phosphatase	5-12	85.18	41.9	0.045
	21-27			
WBC	21-27	10.5	4.3	0.018
	5-12			
	21-27	9.7	3.8	0.013
	13-20			

WBC: White Blood Cells, SE: Stander Error, P value significance≤0. 005.

Table 4 present the relationship between serum ferritin levels with patients age and gender. Eta squared (η^2) is a statistical measure that helps us to understand the strength of the relationship between two variables. It tells us how much of the variance in one variable is explained by the other variable. A higher Eta squared value means that a larger proportion of the variance in one variable is accounted for by the other variable. In other words, it's a measure of how much one variable is related to the other variable.

Table 4: Serum Ferritin relation variance with (Age/Gender)

Association	Eta square(η^2)	Effect	P value
Serum ferritin * age	0.19	Large	0.401
Serum ferritin * gender	0.01	small	0.754

Guide for Eta squared correlation coefficient:

$\eta 2 =$ 0.01 Small effect
$\eta 2 =$ 0.06 Medium effect
$\eta 2 =$ 0.14 Large effect

Cohen's d is a way to measure the size of the difference between two groups, such as the treatment group and the control group in a study. It's a number that tells you how much two groups differ from each other, taking into account the variability within each group. A higher Cohen's d value means a larger difference between the groups.

It is a way to understand the practical significance of the difference between two groups, rather than just the statistical significance. Table 5 below explain clear details about differences in biomarkers under study before and after treatment with Deferasirox.

Table 5: Variability Associated between before and after treatment

Association		Cohen d value	effect
Serum ferritin		0.15	Small
Blood urea		0.27	Small
Serum creatinine		0.7	Medium
ALP		0.37	Small
ALT		0.38	Small
AST		0.06	Small
WBC		0.15	Small

ALP: Alkaline phosphatase, ALT: Alanine Transaminase, AST: Aspartate Transaminase, WBC: White Blood Cells.
Guide for Cohen d correlation coefficient:
d = 0.2 Small effect
d = 0.5 Medium effect
d = 0.8 Large effect

Discussion

Treatment of thalassemia is through the use of iron chelators (deferiprone, deferoxamine, and deferasirox). Deferasirox is proven to be the best for patient compliance because it is taken orally once daily via oral-dispersible .The total number of patients were 100, 49 being male and 51 being female (Table 1). Medical records were collected for each patient, and the age range for the patients were 5 to 27 years of age. The mean age of all patients was 16 years (± 5.2 years). Therefore, patients were separated into 3 groups based on age.

- Ages 5-12
- Ages 13-20
- Ages 21-27

The mean of the following parameters was recorded at baseline, and after Rx (treatment with Deferasirox) along with the standard deviation (Table 2). The biomarkers of white blood cells, AST, and Serum ferritin did not show statistical significance.

The biomarkers of ALT, ALP, and serum creatinine showed strong correlation between basal measurement and after treatment. It is clear that Deferasirox is very likely to raise Serum creatinine in patients after treatment (basal: 0.41 mg/dL ± 0.15 mg/dL versus after Rx: 0.64 mg/dL ± 0.31 mg/dL), it is one of the most mentioned adverse effects concerning Deferasirox, and if it rises above normal significantly the patient may require a dose readjustment, and the dose will be reduced. ALT and Alkaline phosphate also showed an increasing trend after treatment (ALT basal: 22.2U/L ± 11.5U/L versus ALT after Rx: 33.8U/L ± 27.7U/L) and (Alk ph basal: 151.5U/L ± 75.5U/L versus Alk ph after Rx: 202.7U/L ± 109.1U/L; however, AST did not show significant correlation. Blood urea nitrogen showed an increasing trend as well (basal: 22.9mg/dL ± 10.1mg/dL versus after Rx: 27mg/dL ± 8.6mg/dL) statistically significant p value is 0.007 which also indicate renal injuries.

The mean difference for each of blood urea, alkaline phosphate, and white blood cells based on age category were shown in Table 3.

Table 4 shows the correlation between alkaline phosphate and white blood cells and independent parameters, which are age and gender. Alkaline phosphate was shown to be lower in younger patients; however, gender did not affect the parameter. The same phenomenon can be seen with white blood cells, there was a correlation between higher WBC readings and older patients.

For serum ferritin, the Eta association was calculated based on independent variables, which are age and gender (Table 5). The Eta association, meaning the relation of variance between Serum ferritin and age showed a large effect making it statistically

significant. However, there was not a meaningful relation of variance based on gender.

In Table 5, the Cohen d association value was calculated for all parameters, and all showed ≤ 0.2 value which indicated a small effect between basal and after treatment measurements, with the exception of serum creatinine, which had a Cohen d value of 0.7 that showed a nearly large effect on pre and post measurements. The main biomarker that is used to measure the efficacy of Deferasirox is serum ferritin. The process of iron chelation and its effectiveness is measured by the serum ferritin in the blood. In the table results, it is shown that Deferasirox showed a small yet considerable decrease in serum ferritin in patients. Deferasirox played a stabilizing role rather than decreasing serum ferritin to the normal range, in fact almost all patients had serum ferritin levels 10 times the normal range. the findings of the present study are agree with previous study carried out in Tiwans National Health Insurance database, since it finds that the use of Deferasirox for long time can lead to renal toxicity and, liver disease, and hepatic necrosis. These effects usually measured by examining the levels of hepatic and renal enzymes and other function tests in addition to histological studies (19). Other cross sectional study carried out in Iraq by a scientific team indicate that treatment of patient with B- thalassemia by Defrasirox or Defraxmine is associated with high risk of renal and hepatic health problem in the future. There for, it need routine monitor of these vital organs during treatment period (20). On other hand, other studies stated that Deferasirox is the best oral administered iron –chelator agents that is well tolerated by the patients as one-daily oral dose with high grade of efficacy and safety at least when use for less than five years (21). The mechanism of nephrotoxicity by Deferasirox is not well clear, but tubular cell injuries, proximal tube dysfunction and reducing the Glomular Filtration Rate are the main effect that need routine follow- up to prevent serious renal damage (13). Elevated hepatic enzyme levels(ALP and ALT) in patient with B- thalassemia received Deferasirox suggest hepatic cell injuries either by iron

overload or by the drug, in both cases it required periodic- follow up (22). Decreasing serum ferritin level is great when associated with age, that mean Deferasirox have a real good effect in reducing iron over load since iron overload usually leading to high ferritin levels, so it could be used as an indicator of Deferasirox efficacy. However, this effect is not statistically significant in different sex (23). By using Cohen d test, the most effect of Deferasirox in the participated patients was small before and after taken the drug, this may related to the period of drug administration, patient compliance to the drug regimen and the number of the data. White Blood Cells and Blood urea where not significantly affected by using Deferasirox and this mean that no signs of inflammation or serious cell injuries were observed in patients under study and this may related to the protective effect of Deferasirox agent.

Conclusion and Recommendations

Thalassemia is an inherited blood disorder that occurs when the body does not produce enough hemoglobin, an important component of red blood cells.

IpJade (locally manufactured deferasirox in Iraq) is shown to be well tolerable in patients, and efficacious enough to reduce and stabilize serum ferritin levels in patients in all age groups. The main adverse effect that was observed the potential rise in serum creatinine and urea in patients. Of all 100 patients, only 9 patients required a dose reduction because they experienced severe side effects. In addition to hepatic effect which require periodic monitoring.

IpJade is preferred for B-thalassemia patients because of the good patient compliance. Dosages were calculated based on weight and serum ferritin, as well as monitoring parameters incase markers rise (or fall) from the normal or accepted range (24).

Conflict of interest

The authors declare that they have no conflict of interest.

Source of supply

Self-funded study.

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