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Isdeferasirox as Effective as Desferrioxamine in Treatment of Iron Overload in Patients with Thalassemia Major?

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Abstract: *Iron overload may play an important role in increasing morbidity and mortality in patients with thalassemia major.In transfusion-dependent thalassemia, iron-chelation therapy is themain choice to decrease iron burden. Deferasirox (DFX) and desferrioxamine (DFO) were recognized as main chelators in the novel history of iron chelation therapy in thalassemic patients. Deferasirox was the latest up to date iron chelation drug, which was given orally, while parenteral desferrioxamine was the first used one historically. This study aimed to evaluate iron chelation performance of DFX in comparison with DFO in beta-thalassemia major patients. Throughout a 12 months' period, beta- thalassemia major patients whom were regularly followed up in the biggest thalassemia center in Iraq were studied retrospectively, and divided into two categories according to iron chelating drug used.Patients on DFX and DFO were 1083 and 317, respectively. Serum ferritin reduction after one year was comparable for both groups, but a significant lowering in LIC was achieved by DFX. Again; non-significant results of LVEF were found. Patients decided to stop taking DFO more significantly than DFX. We reached a conclusion that deferasirox had a higher potential as an iron chelation therapy when matched with desferrioxamine.*

Keywords:*Deferasirox, desferrioxamine, iron overload, Thalassemia major.*

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I. Introduction

Thalassemias are inherited disorders that result in the decreased synthesis or complete absence of the beta or alpha globin chains of hemoglobin. Patients required chronic blood transfusions, which in turn may lead to chronic iron overload, that if left without a possible management could drive the road to chronic morbidity, and mortality, as iron accumulation is unavoidable event in thalassemia major patients.[1,2]Iron burden is the main cause of complications in transfusion-dependent thalassemia (thalassemia major), including cirrhosis of the liver, endocrine, and heart problems. [2,3]Liver iron concentration (LIC) levels and serum ferritin readings are good reflection to iron overload, which are usually evident after a single or a couple of years following regular blood transfusion initiation. [4,5]A great improvement in the survival of patients with thalassemia had been linked to iron chelation therapy[6], where the body has no active mechanism to excrete accumulated iron, which leads to tissue damage. [7,8]Deferasirox is a member of a new class of tridentates iron chelators, given orally once daily, has a half-life ($t_{1/2}$)of 8 – 16 hours.Glucuronidation with hepatobiliary excretion into stool is the usual path by which metabolism and elimination of the drug with iron chelate have taken place. Deferasirox enters cells to remove iron. [9,10]

Desferrioxamine (DFO)mesylate (or sometimes called deferoxamine) isa naturally occurring trihydroxamic acid produced by Streptomyces pilosus, iron excretion is stimulated into urine in patients with thalassemia major. It has a positive effect on morbidity and mortality in iron overloaded thalassemia patients. Nevertheless; patients are poorly adhered to treatment because it has to be given by slow subcutaneous or intravenous infusion (through a pump) over 8 to 12 hours, 5 to 7 nights a week. [10,11]In Iraq, according to our observations, all hereditary anemia centers were used to use desferrioxamine (DFO) as a sole iron chelation therapy till late 2010, where deferasirox (DFX) was recently started for some patients, and since that time, this drug is involved in practice progressively as it was orally administered rather than previous iron chelator which was given parenterally.[12]

II. Aim of the study

Trying to investigate the ability of deferasirox and desferrioxamine in terms of iron chelation and related parameters.

III. Patients & Methods

Beta-thalassemia major patients whom regularly visited Hereditary Anemia Center at Ibn Albaladi Hospital in Baghdad were evaluated for 12 months in this retrospective, single center study which started on 1st of July 2016 and ended on 30th of June 2017.All patients should be ≥2 years old, andreceived regular (frequent) red blood cell transfusions (at least once each 5-6 weeks).Patients were divided into 2 groups according to iron chelation type; first group contained patients taking deferasirox (Exjade, Novartis), while patients on desferrioxamine (desferal,Novartis) were representing the second group, both drugs were supplied free of charge through Iraqi ministry of health.At the start of this study, all involved patients had serum ferritin levels >1000 μg/L, free of renal complications (serum creatinine less than upper normal limit (UNL) through laboratory parameters), and with normal platelet count (150000 – 400000 /mm3).

Echocardiography study readings were documented; measurements of left ventricular ejection fraction (LVEF) were categorized according to Westwood criteria: lower normal limit 59 for males, and 63 for females. [13]Patients whom had alanine aminotransferase (ALT) levels more than 5 times the upper normal limit were out of the study from the start.Total iron overload was monitored by measuring serum ferritin levels before and 3-monthly after starting iron chelation therapy, and liver iron concentration (LIC) measured through magnetic resonance imaging (MRI), done at baseline and after one year.In both groups, dose of deferasirox was 20 - 40 mg/kg/day orally, and for desferrioxamine, it was 30 – 60 mg/kg/day subcutaneously over 8 – 12 hours, 5- 7 times per week,depending on number of transfusions and pre- dose serum ferritin levels according to attending physician`s decision, in line with TIF (Thalassemia International Federation) guidelines. [14]Every patientwas monitored monthly by a complete medical history, and physical examination,accomplished by attending hematologist.Compliance of registered patients was assessed by mandatory return back of empty packages and direct interview with the treating physician, which was documented in medical files.Statistical work was analyzed using SPSS (Statistical Package for the Social Sciences), version 22,all required tests were used as needed during analysis process. To reach a level of statistical significance, p- value should be ≤ 0.05.

IV. Results

Total number of patients on deferasirox was 1406, while patients who met our inclusion criteria were 1083; 585 (54.02%) were males, and 498 (45.98%) were females. The other group of patients on desferrioxamine whom in parallel with above criteriahad 317 patients out of a total 423 patients, 169 (53.31%) were males, and 148 (46.69%) were females.Patients from both groups had comparable general characteristics without touching a statistical significance (p value > 0.05), such as age, male : female ratio, pre-transfusion hemoglobin level, and other parameters mentioned in Table (1).

Table (1): General characteristics of patients

Variable, mean ± SD	Deferasirox group (1083), n (%)	Desferrioxamine group (317), n (%)	P- value
Age (years)	15.6 ± 3.4	16.1 ± 3.2	0.0198
Male : female (%)	54.02 : 45.98	53.31 : 46.69	0.8236
Pre-transfusion hemoglobin (g/dl)	7.8 ± 0.9	7.5 ± 0.8	0.1688
Total transfusions received during study period	14.7 ± 1.2	14.9 ± 1.4	0.0122
Previous combination iron chelating therapy, n (%)	55 (5.08%)	26 (8.20%)	0.0365

Serum ferritin in deferasirox (DFX) group was started with a level of 1924μg/L to reach 1384 at the end of study period (EOS). Desferrioxamine (DFO) group ranged from 2341 till 1747μg/L after one year.Doses of DFX and DFO were between 35.6, 49.7, at the start, and 38.6, 56.2, at the end of study (EOS), respectively. More details are in Table (2).

Table (2): Time table of serum ferritin with doses of DFX and DFO

Time	Deferasirox (DFX) group: mean serum ferritin, μg/L (1083)	DFX dose, mg/ kg/ day, mean ± SD	Desferrioxamine (DFO) group: mean serum ferritin, μg/L (317)	DFO dose, mg/ kg/ day, mean ± SD
Baseline	1924 ± 38.8	35.6 ± 1.2	2341 ± 57.9	49.7 ± 0.9
3 months	2037 ± 35.6	39.3 ± 1.6	2118 ± 48.5	53.4 ± 0.3
6 months	1857 ± 42.3	38.4 ± 1.7	2019 ± 52.1	57.8 ± 0.4
9 months	1572 ± 37.4	37.8 ± 1.5	1853 ± 53. 4	55.6 ± 0.5
12 months	1384 ± 33.2	38.6 ± 1.8	1747 ± 43.2	56.2 ± 0.8

Statistically significant (p value < 0.0001) net reduction in serum ferritin in deferasirox (DFX) group was 540 (28.07%) *µ*g/L, while other group of desferrioxamine (DFO) had also a significant net reduction (p value < 0.0001), which was 594 (25.37%) *µ*g/L. However; p- value between the groups was (0.3436) using paired t- test, whichcould not reach statistical significance, so; no drug was superior over the other one in serum ferritin reduction, with some favorability towards DFX. These resultsare simplifiedin figure (1).

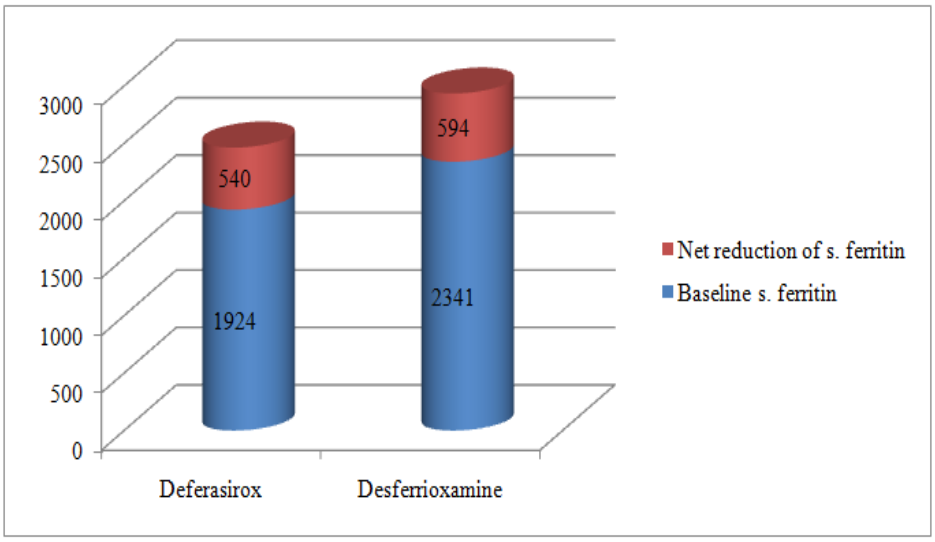

Fig. 1: Net reduction of serum ferritin in both groups of patients

Liver iron concentration (LIC), in mg/ g Fe dry weight measured by Magnetic Resonance Imaging technique (MRI), was decreased in DFX group from 16.7 to reach 11.4 after one year. Patients treated with DFO showed LIC of 13.2 at the end of our study out of a baseline reading of 16.1. Based on these LIC values that were illustrated in figure (2); DFX had a statistically significant power (p < 0.0001) to lower iron in the liver more than DFO, when applying a matched samples t-test.

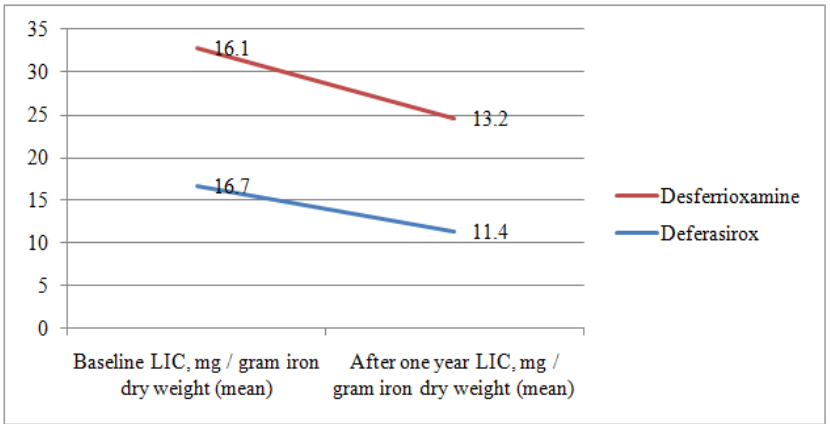

Fig. 2: LIC mean (mg/ gram Fe dry weight) at baseline and end of study period

Left ventricular ejection fraction (LVEF) measurements after one year (EOS) treatment with DFX and DFO were close to each other, without a statistical significance, in spite of a slight increase in frequency of patients < lower limit described byWestwood [12], where odds ratio > 1, as shown in Table (3), which pointed out to more patients who had < lower limit of LVEF within deferasirox group.

Table (3): Comparison of LV ejection fraction after DFX, and DFO treatment

Left ventricularejection fraction after one year (EOS), n (%):	DFX group (1083), n (%)	DFO group (317), n (%)	Odds ratio	95% CI (confidence interval)	P- value
• < lower limit*	174 (16.07%)	47 (14.83%)	1.0996	0.7752 to 1.5600	0.5944
• ≥ lower limit*	909 (83.93%)	270 (85.17%)	0.9094	0.6410 to 1.2901	

* Westwood criteria: lower normal limit is 63 for females**,** and 59 for males.

Table (4) is concerned with compliance of our patients, regarding interim or constant drug stoppage. Patient`s own viewpoint was a statistically significant cause after which DFO was halted more frequently, while physician`s saw (whatever the cause was) did not reach significance.

Table (4): Causes of temporary pause in iron chelation therapy

Cause of transient therapy cessation, n (%):	DFX group (1083), n (%)	DFO group (317), n (%)	Odds ratio	95% CI (confidence interval)	P- value
• Physician`s decision, n (%)	54 (4.99%)	14 (4.42%)	1.1358	0.6223 to 2.0729	0.6783
• Patient`s own opinion, n (%)	33 (3.05%)	39 (12.30%)	0.2240	0.1383 to 0.3628	< 0.0001

V. Discussion

This study discussed the use of deferasirox (DFX) and desferrioxamine (DFO) in the management of iron overload in beta-thalassemia major.It is important to have a glance on the Iraqi experience putting in mind the available resources, as there are no published papers about Iraqi patients yet, and even at other parts of the world with such a big number of patients involved.Desferrioxamine (DFO) was the only used iron chelation therapy in Iraq for many years,but compliance with the parenteral desferrioxamine (DFO) has proved struggling to all patients with transfusional iron overload.[10,15]Recent development of deferasirox (DFX) as it wasgiven orally rather than by injections, had made a revolution in the management of iron overload in these patients. [10,16]In the current study, patients who took deferasirox (DFX) and desferrioxamine (DFO) had alike (statistically non-significant) general features, including age, sex ratio, pre-transfusion hemoglobin concentration, total transfusions received during study period, and previous combination iron chelating therapy, this may be important to decrease any bias regarding iron overload appeared results. The presence of more than one iron chelator would give a treating physician more options to respond to different iron overload requirements, so that; having a similar effect on different body organs when using different chelators, was considered as avital issue of concern. Advances in treatment approaches led to a closer survival rate of thalassemia major cases to that of thalassemia intermedia.[17,18]

Our results corroborated the above opinions, when talking about serum ferritin and LIC, which reflected patient`s body iron overload response to chelation therapy. [14,19]Less magnitude of serum ferritin was noted in deferasirox group of patients; however; it did not catch significance. This was also mentioned by another investigator [20], where deferasirox was more effective in eliminating iron load than desferrioxamine in hemolytic anemias. [21,22]Some authors suggested that treatment adherence with deferasirox may be better than that of desferrioxamine (DFO), and thus it should have led to improved long-term outcomes in transfusional hemosiderosis [23].Even less optimistic authors said that deferasirox (DFX) had been shown to be as effective as desferrioxamine(DFO) with a favorable safety profile in patients with different hemoglobinopathies.[20,24-26]LIC (liver iron concentration) was used to assess severity of iron burden in thalassemic patients, it correlated with serum ferritin, but also considered as a bad predictor of ferritin in some types of thalassemia, even in transfusional dependent patients.[5,27]Deferasirox patients in our sample had lower LIC readings after one year of chelation, proved by a statistical significance, animal research reports [28], as well as human's data [29], moved forward with our results, but other workers stated a contradictory view, with lower serum ferritin measures and LIC when using DFO. This might be justified by lower starting ferritin readings in DFO group of patients more than DFX within their published data. [17]MRI T2* technique used to measure cardiac iron accumulation [30], was not widely available in our center, echocardiography evaluation to measure left ventricular diastolic function as an early sign of cardiac iron overload, was monitored instead. [13,29]Analogous results of LVEF were found, which means both chelators had a good impact on myocardial iron load. This was supported by other writers.[13,31]

From our statistically significant point of view, patients preferred to stop taking DFO more than DFX, which might be related to DFO parenteral method of administration, affecting their compliance, efficacy, and overall performance. [10,32,33]Standing on above details when comparing DFX with DFO in thalassemia patients; "a trend toward superiority for deferasirox" was felt by authors of CORDELIA study, while Al-Kuraishyetal. published a clear statement that favored deferasirox over desferrioxamine regarding iron chelation. [22,31]

VI. Conclusion

A more potent, stable, and tolerable removal of excess body iron was fulfilled using deferasirox, rather than desferrioxamine.

References

[1]. Delea TE, Edelsberg J, Sofrygin O, et al. Consequencesand costs of noncompliance with ironchelation therapy in patients with transfusion dependent thalassemia: a literature review Transfusion. 2007;47(10):1919-1929.

[2]. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complications of beta-thalassemia major in North America. Blood. 2004;104(1):34- 39.

[3]. Rund D, Rachmilewitz E. B-thalassemia. N Engl J Med. 2005;353(11):1135-1146.

[4]. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood.1997;89: 739-761

[5]. Porter JB, Elalfy M, Taher A, Aydinok Y, Lee SH, Sutcharitchan P, El-Ali A, Han J, El-Beshlawy A. Limitations of serum ferritin to predict liver iron concentration responses to deferasirox therapy in patients with transfusion-dependent thalassaemia. European journal of haematology. 2017 Mar 1;98(3):280-8.

[6]. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004;89(10): 1187-1193.

[7]. El Safy UR, Fathy MM, Hassan TH, Zakaria M, Al Malky MA, Arafa M, El Sayed H, Al Ghobashy A, Zaho B, Wahab AA, Mourad MH. Effect of breastfeeding versus infant formula on iron status of infants with beta thalassemia major. International breastfeeding journal. 2017 Apr 17;12(1):18.

[8]. Piga A, Bejaoui M, Kilinc Y, Perrotta S, Vichinsky E, Arrowsmith-Bensasson C, Glimm E, Alberti D. Long-Term Treatment with the Once-Daily Oral Iron Chelator Deferasirox (Exjadereg], ICL670) Is Effective and Generally Well Tolerated in Pediatric Patients.

[9]. Glickstein H, Ben El R, Shvartsman M, Cabantchik ZI. Intracellular labile iron pools as direct targets of iron chelators: a fluorescence study of chelator action in living cells. Blood. 2005;**106**: 3242-3250.

[10]. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, Aydinok Y, Kattamis A, Kilinc Y, Porter J, Capra M. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia. Blood. 2006 May 1;107(9):3455-62.

[11]. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. New England Journal of Medicine. 1994 Sep 1;331(9):567-73.

[12]. Al-Allawi NAS, Jalal SD, Mohammad AM, Omer SQ, Markous RSD. β-thalassemia intermedia in Northern Iraq: A single center experience. Biomed Res Int. 2014;2014.

[13]. Westwood MA, Anderson LJ, Maceira AM, Shah FT, Prescott E, Porter JB, Wonke B, Walker JM, Pennell DJ. Normalized left ventricular volumes and function in thalassemia major patients with normal myocardial iron. Journal of Magnetic Resonance Imaging. 2007 Jun 1;25(6):1147-51.

[14]. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the management of transfusion dependent thalassaemia (TDT). Nicosia (CY): Thalassaemia International Federation; 2014.

[15]. Arboretti R, Tognoni G, Alberti D. Pharmacosurveillance and quality of care of thalassaemic patients. Eur J Clin Pharmacol.2001;**56**: 915-922.

[16]. Davies GI, Davies D, Charles S, Barnes SL, Bowden D. Successful Desensitisation to Deferasirox in a Paediatric Patient with β Thalassemia Major. Pediatric Allergy and Immunology. 2017 Mar 1.

[17]. Pepe A, Meloni A, Capra M, Cianciulli P, Prossomariti L, Malaventura C, Putti MC, Lippi A, Romeo MA, Bisconte MG, Filosa A. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. haematologica. 2011 Jan 1;96(1):41-7.

[18]. Di Maggio R, Maggio A. The new era of chelation treatments: effectiveness and safety of 10 different regimens for controlling iron overloading in thalassaemia major. British Journal of Haematology. 2017 Apr 25.

[19]. Kwiatkowski JL. Current recommendations for chelation for transfusion-dependent thalassemia. Annals of the New York Academy of Sciences. 2016 Mar 1;1368(1):107-14.

[20]. Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, Gattermann N, Giraudier S, Lee JW, Chan LL, Lin KH. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. haematologica. 2010 Apr 1;95(4):557-66.

[21]. Vichinsky E, Torres M, Minniti CP, Barrette S, Habr D, Zhang Y, Files B. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. American journal of hematology. 2013 Dec 1;88(12):1068-73.

[22]. Al-Kuraishy HM, Al-Gareeb AI. Comparison of deferasirox and deferoxamine effects on iron overload and immunological changes in patients with blood transfusion-dependent β-thalassemia. Asian journal of transfusion science. 2017 Jan;11(1):13.

[23]. Vichinsky E, Pakbaz Z, Onyekwere O, Porter J, Swerdlow P, Coates T, Lane P, Files B, Mueller BU, Coïc L, Forni GL, Fischer R, Marks P, Rofail D, Abetz L, Baladi JF (2008) Patient-reported outcomes of deferasirox (Exjade, ICL670) versus deferoxamine in sickle cell disease patients with transfusional hemosiderosis. Substudy of a randomized open-label phase II trial. ActaHaematol 119:133–141

[24]. Voskaridou E, Plata E, Douskou M, Papadakis M, Delaki EE, Christoulas D, Terpos E (2010) Treatment with deferasirox (Exjade®) effectively decreases iron burden in patients with thalassaemia intermedia: results of a pilot study. Br J Haematol 148:332–334.

[25]. Vichinsky E, Onyekwere O, Porter J, Swerdlow P, Eckman J, Lane P, Files B, Hassell K, Kelly P, Wilson F, Bernaudin F, Forni GL, Okpala I, Ressayre-Djaffer C, Alberti D, Holland J, Marks P, Fung E, Fischer R, Mueller BU, Coates T, Deferasirox in Sickle Cell Investigators (2007) A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol 136:501–508

[26]. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, Marchetti M, Piga A, Tura S (2008) Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. Haematologica 93:741–752

[27]. Pakbaz Z, Fischer R, Fung E, Nielsen P, Harmatz P, Vichinsky E. Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients. Pediatric blood & cancer. 2007 Sep 1;49(3):329-32.

[28]. Nick H, Wong A, Acklin P, Faller B, Jin Y, Lattmann R, Sergejew T, Hauffe S, Thomas H, Schnebli HP. ICL670A: preclinical profile. Iron Chelation Therapy. 2002:185-203.

[29]. Wood JC, Otto-Duessel M, Gonzalez I, Aguilar MI, Shimada H, Nick H, Nelson M, Moats R. Deferasirox and deferiprone remove cardiac iron in the iron-overloaded gerbil. Translational research. 2006 Nov 30;148(5):272-80.

[30]. Fragasso A, Ciancio A, Mannarella C, Gaudiano C, Scarciolla O, Ottonello C, Francone M, Nardella M, Peluso A, Melpignano A, Veglio MR. Myocardial iron overload assessed by magnetic resonance imaging (MRI) T2* in multi-transfused patients with thalassemia and acquired anemias. European journal of internal medicine. 2011 Feb 28;22(1):62-5.
[31]. Pennell DJ, Porter JB, Piga A, Lai Y, El-Beshlawy A, Belhoul KM, Elalfy M, Yesilipek A, Kilinç Y, Lawniczek T, Habr D. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). Blood. 2014 Mar 6;123(10):1447-54.
[32]. Cohen A. Management of iron overload in the pediatric patient. Hematology/oncology clinics of North America. 1987 Sep;1(3):521-44.
[33]. Chang HH, Lu MY, Peng SS, Yang YL, Lin DT, Jou ST, Lin KH. The long-term efficacy and tolerability of oral deferasirox for patients with transfusion-dependent β-thalassemia in Taiwan. Annals of hematology. 2015 Dec 1;94(12):1945-52.

*Hayder H Al-Momen. " Is deferasirox As Effective As Desferrioxamine in Treatment of Iron Overload In Patients With Thalassemia Major?." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.8 (2017): 29-34