Al-Mustaqbal Journal of Pharmaceutical and Medical Sciences

Volume 2 | Issue 1 Article 4

2024

A Study of Serum Levels of Ferritin, Hepatic and Renal functions in Beta-Thalassemia Major (BTM) Patients Treated With Deferasirox (DFX) Tablets, Desferioxamine (DFO) Vial, or Combination of Both (DFX + DFO) in Thalassemia Center/Karbala

Shereen M. Mekkey
College of Pharmacy, Al-Mustaqbal University, Babylon, 51001, Iraq, shereen.mohammed@uomus.edu.iq

Maysam Ali Ameen
Al-Safwa University College, Pharmacy Department, maysem.ali@alsafwa.edu.iq

Najwa Kahtan Hadi
Al-Safwa University College, Pharmacy Department, najwa.kahtan@alsafwa.edu.iq

ISSN: 2959-8974 – e-ISSN: 3006-5909

Recommended Citation

Mekkey, Shereen M.; Ameen, Maysam Ali; and Hadi, Najwa Kahtan (2024) "A Study of Serum Levels of Ferritin, Hepatic and Renal functions in Beta-Thalassemia Major (BTM) Patients Treated With Deferasirox (DFX) Tablets, Desferioxamine (DFO) Vial, or Combination of Both (DFX + DFO) in Thalassemia Center/ Karbala," *Al-Mustaqbal Journal of Pharmaceutical and Medical Sciences*: Vol. 2 : Iss. 1 , Article 4. Available at: https://doi.org/10.62846/3006-5909.1008

AL-MUSTAQBAL JOURNAL OF PHARM. & MED. SCIENCES 2024;2:37–43

ORIGINAL STUDY

A Study of Serum Levels of Ferritin, Hepatic and Renal functions in Beta-Thalassemia Major (BTM) Patients Treated With Deferasirox (DFX) Tablets, Desferioxamine (DFO) Vial, or Combination of Both (DFX + DFO) in Thalassemia Center/Karbala

Shereen M. Mekkey [a,*], Maysam Ali Ameen [b], Najwa Kahtan Hadi [b]

[a] College of Pharmacy, Al-Mustaqbal University, Babylon, 51001, Iraq
[b] Al-Safwa University College, Pharmacy Department

ABSTRACT

A category of inherited blood illnesses known as beta-thalassemias are defined by abnormalities in the synthesis of hemoglobin beta chains, which can result in a wide range of phenotypes, from severe anemia to people who show no symptoms at all. People who have thalassemia major typically experience severe anemia during the first two years of life, necessitating frequent red blood cell (RBC) transfusions.

Management of individuals with β-thalassemia is centered on appropriate, safe blood transfusions (free of transfusion-transmitted illnesses) and prevention of iron excess. Complications from iron overload are brought on by routine transfusion therapy.

This study is a retrospective analysis of a sample of around 75 patients with beta thalassemia major (BTM) who were receiving iron chelation therapy and frequent transfusions at the Thalassemia Center at Children's Hospital in Karbala.

In this study, we compared the long-term effects of different iron chelation regimens (Desferioxamine vial (DFO), Deferasirox tablets (DFX), a combination of both (DFO + DFX)) on iron overload as indicated by serum levels of ferritin, liver and kidney functions.

A significant difference was found among the three treatment protocols in serum levels of ferritin The ferritin levels were (1049μg/L ± 115.5) in DFX tablet treated group, (4325.5μg/L ± 299.8) in e DFO vial treated group; (4988.2 μg/L ± 438.4) in those treated with a combination of both DFX and DFO.

A significant difference was also found in hepatic function tests among the three treatment protocols as indicated by serum levels of glutamic-oxaloacetic transaminase (GOT) and Glutamic-pyruvic transaminase (GPT). For those treated with DFX tablet (GOT level expressed in units/Liter are (24.51 ± 1.86) and GPT level (18.72 ± 2.07)), for those treated with DFO vial (GOT level (28.05 ± 2.39) and GPT level (29.57 ± 2.54)); for those treated with combination therapy of both DFO + DFX (GOT level (31.15 ± 2.06) and GPT level (31.99 ± 2.23).

No significant difference was found among the three treatment protocols in renal functions test as indicated by urea and creatinine serum levels.

In conclusion those treated with DFX had considerably lower serum ferritin levels than those treated with DFO alone or in combination with DFX. While there were no discernible variations in the concentrations of urea and creatinine between the treatment regimens, the liver enzymes of those treated with DFO + DFX were significantly higher.

Keywords: Ferritin, Hepatic function, Renal function, DFO, DFX, BTM

Received 9 February 2024; accepted 15 April 2024.
Available online 30 May 2024

* Corresponding author.
E-mail addresses: shereen.mohammed@uomus.edu.iq (S. M. Mekkey), maysem.ali@alsafwa.edu.iq (M. A. Ameen), najwa.kahtan@alsafwa.edu.iq (N. K. Hadi).

https://doi.org/10.62846/3006-5909.1008

1. Introduction

A diverse collection of genetic illnesses known as thalassemias are caused by a reduction in the production of either the alpha or beta chains of hemoglobin (Hb). The oxygen-carrying protein in red blood cells is called hemoglobin. There are two proteins in it: an alpha and a beta. The inability of the organism to produce enough of either of these two proteins results in improper red blood cell formation and insufficient oxygen transport, which leads to anemia, a condition that manifests in early childhood and persists throughout life [1].

The degree of thalassemia affects the clinical characteristics. In severe cases, there may be growing jaundice, inability to thrive, and bony abnormalities such as frontal bossing, large malar eminence, maxillae hypertrophy, and lengthy bone deformities resulting from bone marrow expansion. Milder forms of thalassemia are more subtle and present with fatigue and weakness [2]. Thalassemia is subdivided into α-thalassemia and β-thalassemia, depending on the underlying genetic mutation and affected globin-chain subunits within the hemoglobin tetramer [3].

β-thalassemia is either homozygous or double heterozygotes for mutations in the β-globin gene. The disease harshness is influenced by the type of mutation in the β-globin gene and the impairment scope of β-globin chain productin [3].

β-thalassemia can be classified as transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) according to the severity of anemia and the need for transfusions [3].

Apoptosis and oxidative cell damage are caused by reactive oxygen species formed by excess unpaired and insoluble α globin chains that accumulate at the red cell precursors membrane and free iron in β-thalassaemia major (BTM). This occurs within the erythropoietic tissue, leading to mature red cell hemolysis and inefficient erythropoiesis (IE) [4].

In β -thalassaemia major (BTM), the excess unpaired and insoluble α globin chains precipitate at the red cell precursors membrane and free iron catalysis the formation of reactive oxygen species leading to oxidative cell damage and premature cell death by apoptosis. Ineffective erythropoiesis (IE) and hemolysis of mature red cells are the outcomes of this occurring within the erythropoietic tissue [4].

Although the bone marrow produces more red blood cells faster than it would otherwise, this is insufficient to prevent severe anemia. Heme is released when erythrocytes break down, increasing the gastrointestinal tract's absorption of iron [5]. Inadequate hepcidin suppression leads to high iron absorption (a protein that controls the duodenal intake of iron). Iron overload is the result of regular blood exchange and increased erythropoiesis [6].

1.1. Therapy of β-thalassemia

1.1.1. Blood transfusion (essential, lifesaving therapy in β-thalassemia)

Blood transfusions compensate for chronic anemia, prevent bone deformities, facilitate normal growth and activity levels, and allow patients to have a good quality of life (QoL). Transfusions provide fresh, normal RBCs that correct anemia and suppress ineffective erythropoiesis, which helps to prevent hepatosplenomegaly and limit bone marrow hyperplasia [7].

Leukoreduced packed red blood cells (RBCs) are recommended for patients with β-thalassemia. Anemia and/or clinical symptoms should be taken into consideration when deciding whether to begin blood transfusions [8].

Patients with BTM experience iron overload as a result of blood transfusions, which provide the patient's body with 200–250 mg of iron per unit. Overexposure of iron to organs such the liver, heart, and endocrine system can cause these organs to malfunction [9].

Because of its high reactivity, unbound iron can react with oxygen to produce inflammation. Additionally, it contributes to the overproduction of free radicals, which damage biological components.Excess iron can be efficiently removed using chelation therapy. Currently on the market, two chelating medications that bind to Fe^{+} molecules and excrete them through urine or feces are (DFX) and (DFO) [10].

Determining whether transfusions are necessary and beneficial depends on assessing for known thalassemia consequences, such as anemia and poor erythropoiesis. To determine whether chelation is necessary and to gauge the effectiveness of continuous chelation therapy, patients with both TDT and NTDT must have their level of iron excess assessed. Lastly, check for recognized toxicities of chelators [11].

The liver is the only place where transferrin and ferritin production occurs and where iron is mostly stored. Although there are several contributing factors to liver injury, iron excess is thought to be the primary one. Iron is often stored in the liver as protein-bound iron, which can be extremely hazardous in situations of iron excess and act as a catalyst for the formation of free radicals, which can lead to lipid peroxidation and hepatotoxicity. Elevated levels of the liver enzymes aspartate transaminase (AST), also known as GOT, and alanine transaminase (ALT),

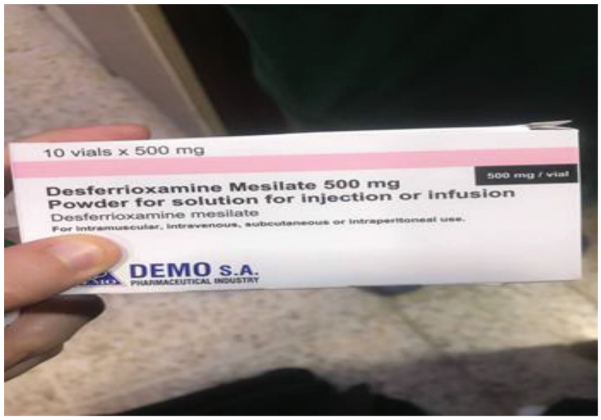

Fig. 1. Desferoxamine (DFO) vial.

Fig. 2. Desferoxamine pump.

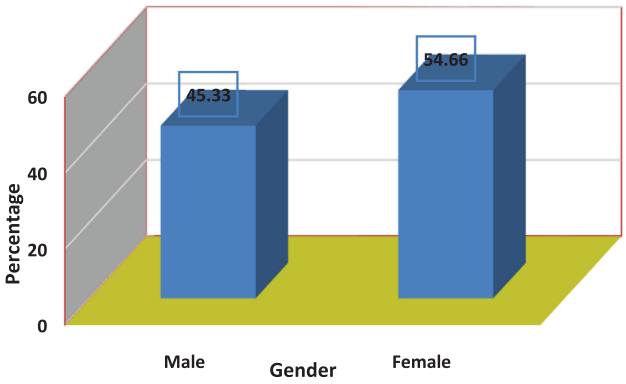

Fig. 3. Percentage of Male and Female participants in the study.

also known as GPT, would follow an acute or long-term liver injury [12].

TDT has been linked to proximal tubular injury, with nearly all patients exhibiting low-molecular-weight proteinuria. The mechanisms linked to iron excess, hypoxia, and chronic anemia may account for tubular injury. Individuals suffering with β-thalassemia have also been found to have abnormal glomerular filtration rates (GFR). Hyperfiltration is frequently associated with anemia [13].

1.1.2. Iron chelation therapies

Most often, treatment for iron chelation is initiated when the serum ferritin level reaches 1000 ng/L, which typically occurs after the tenth or twelfth transfusion [14].

1.1.2.1. Desferioxamine (DFO). DFO improves the removal of free iron from the body mostly in the urine and to a lesser extent in the feces by binding it to the bloodstream in a 1:1 ratio. The medication is sold in vials (Fig. 1). A subcutaneous infusion pump (Fig. 2) is used to administer 40 mg/kg (run 30 to 50 mg/kg) over the course of 8 to 10 hours, at least 5 nights a week. At physiologic pH, a single chelator particle binds a single iron molecule to form the remarkably stable hex dentate complex of iron ferrioxamine [15]. While SC injection of DFO can effectively regulate the iron burden in the liver, it cannot prevent iron deposition in the heart in all individuals [16].

1.1.2.2. Deferasirox (DFX). An oral chelator called DFX is accessible for regular use (Fig. 3). The US Food and Drug Administration (FDA) has approved it for the treatment of secondary iron excess. For children older than two years, DFX is effective over the course of a 24-hour dosage period, and preclinical and clinical evidence suggest that it may be able to effectively remove iron from the liver and heart [17]. These medications have side effects despite their medicinal benefits. Additionally, they may raise liver enzyme and blood creatinine levels, which should be taken into account throughout treatment [18].

Lal *et al.* [19] reported the first instance of DFX and DFO being used simultaneously in 2013. They treated 22 patients with transfusion-dependent thalassemia who also had persistent iron excess or organ damage. The patients were treated safely and effectively. Furthermore, in patients with severe transfusional cardiac siderosis, the Hyperion study demonstrated the safety and effectiveness of combination therapy with DFX plus DFO, followed by monotherapy with DFX [20]. However, the available literature on this combination treatment is limited and varied [21–25].

Hepatic iron may, however, have a propensity to decline in those studies where the impact on heart and liver iron was assessed. Regarding heart iron, the outcomes were more inconsistent. When myocardial T2*, liver iron concentration (LIC), or serum ferritin levels were symptomatic of severe iron accumulation, when monotherapies did not provide optimum chelation, or when deferipron (DFP) was rejected or had

severe adverse effects, the combination of DFX and DFO was taken into consideration [26].

2. Patients and methods

This is a retrospective study that was accomplished from September, 2022 until January, 2023 in Children's Hospital of Karbala/Thalassemia Center.

The study enrolled 75 patients diagnosed with BTM and are regularly treated for several years in the center, they have received at least 10 units of packed red blood cells and have a serum ferritin level of >1000 ng/mL and are not spleenectomized and with no other chronic disease, [25] of them were treated with oral tablts DFX-30 mg/kg, [25] of them were treated with DFO using Sc. pump in a dose of 25 mg/kg, [25] of them received a combination therapy DFO + DFX − (25 mg/kg/d + 30 mg/kg/d) daily.

Serum ferritin levels are measured using a standard enzyme-linked immunosorbent assay (ELISA) kit. Liver function tests, including serum GPT and GOT, renal function tests including urea and creatitnine are measured using standard laboratory techniques.

Patients with unspecified type of hemolytic anemia, spleenectomy, chronic disease, cardiomyopathy were all excluded. Verbal consent was taken from all patients.

The data of the present study was analyzed statistically by SPSS software version 29 using chi-square test and one way ANOVA. The level of significance was set to 5%. $P < 0.05$ was considered significant while $P > 0.05$ was considered as non-significant [26].

3. Results

3.1. Distribution of participants according to the gender and age

According to the study results, a total of 75 individuals were enrolled in this study, the percentage of male participants with BTM was (45.33%), while percentage of female participants with beta-thalassemia major was (54.66%) (Fig. 3), with the highest percentage of participants at age interval (12–21) years old (Fig. 4).

3.2. Comparison of Serum levels of Ferritin among the study groups

In patients treated with deferasirox (DFX), the serum ferritin levels of ferritin expressed as (mean ± SD) and are measured in (μg/L) are (1049 ± 115.5),

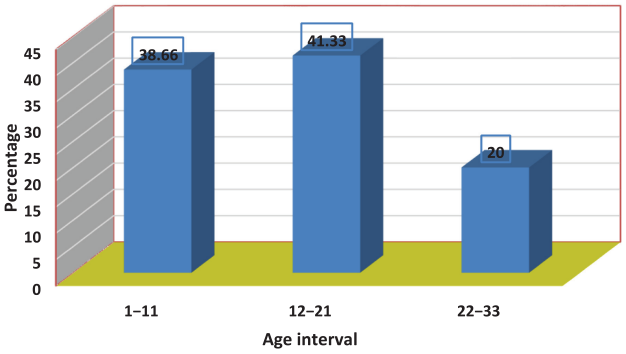

Fig. 4. Percentage of each age interval in the study.

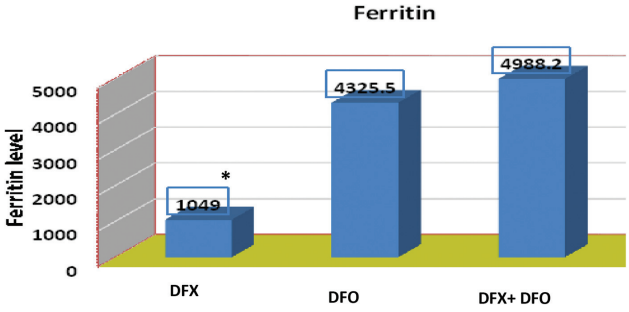

Fig. 5. Serum levels of ferritin expressed in (μg/L) among study groups (DFX, DFO, DFX + DFO).

while for the group treated with deferoxamine (DFO), the ferritin levels are (4325.5 ± 299.8).

For the group treated with a combination therapy (DFX+ DFO), the ferritin levels are (4988.2 ± 438.4) (Fig. 5).

Serum levels of ferritin were significantly lower in those treated with DFX as compared to those treated with DFO alone or in combination with DFX, while no significant difference was found between the DFO treated group and those treated with combination of DFX and DFO (Fig. 5).

3.3. Comparison of liver function tests among the study groups

In the group treated with DFX tablets, the liver GOT level measured in units/Liters was (24.51 ± 1.86) and GPT level measured also in units/Liters was (18.72 ± 2.07).

For patients treated with DFO vial, GOT level was (28.05 ± 2.39) while GPT level (29.57 ± 2.54).

Patient that take combination (DFX tablets + DFO vial); GOT level was (31.15 ± 2.06) and GPT level was (31.99 ± 2.23). Patients treated with combined DFO and DFX has showed a significant increase in liver enzymes as compared to those treated with either DFO or DFX as shown in (Fig. 6A and Fig. 6B).

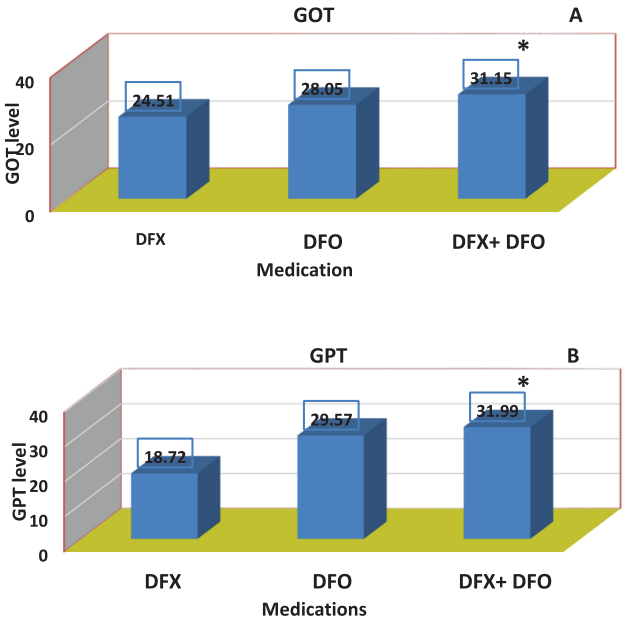

Fig. 6. Serum levels of liver enzymes (GOT, GPT) measured in (Units/Liters) among the study groups (DFX, DFO, DFO + DFX), Fig. 6A refers to GOT levels, Fig. 6B refers to GPT levels.

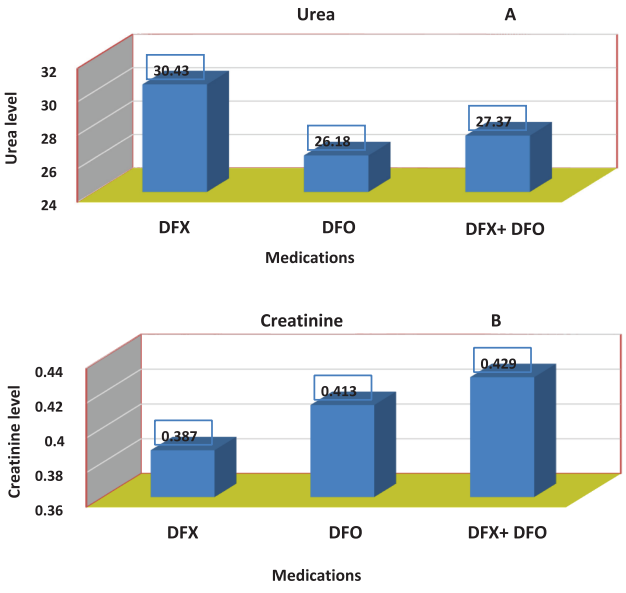

Fig. 7. (A and B): Serum levels of Urea and Creatinine measured in (mg/dl) among the study groups (DFX, DFO, DFO + DFX), Fig. 7A refers to urea levels, Fig. 7B refers to creatinine levels.

3.4. Comparison of kidney function tests among the study groups

Urea and creatinine were measured in units of (mg/dl) as a kidney function tests. In the group treated with DFX tablet; urea level was (30.43 ± 1.88) and creatinine level was (0.387 ± 0.02).

For the group treated with DFO vial, urea level was (26.18 ± 1.78) and creatinine level was (0.413 ± 0.04).

In the group treated with combination of DFO + DFX, urea level was (27.37 ± 1.88) and creatinine level was (0.429 ± 0.03) (Fig. 7).

No significant difference was found among the three study groups regarding the kidney function tests.

4. Discussion

With the ability to measure iron accumulation in the organs directly and the availability of three iron chelators, two of which can be taken orally, most thalassemia patients can now achieve normal or nearly normal levels of serum ferritin and normal concentrations of hepatic and cardiac iron. Additionally, the ability to perform an intense DFP + DFO chelation has raised patient survival rates and allowed for a comparatively quick reduction in iron overload [27].

Nevertheless, in a subgroup of people, difficulties in adhering to chelation therapy or adverse reactions to one or more chelating medicines make it challenging to accomplish the intended outcome, with a risk of incapacitating consequences and a decreased survival rate [25].

This study was conducted to assess the effects of various iron chelation therapy protocols on serum ferritin levels, kidney function tests (urea and creatinine), and liver function tests (GOT, GPT) in a group of BTM patients.

There was no significant difference observed between the DFO treated group and those treated with combination of DFX and DFO, however serum levels of ferritin were significantly lower in those treated with DFX as compared to those treated with DFO alone or in combination with DFX, while no significant difference was found between the DFO treated group and those treated with combination of DFX and DFO.

Ferritin levels will rise in BTM patients who get both DFX and DFO medication, according to research by Ali *et al.* [28], which is consistent with our findings.

Treatments include DFX and DFO in a mouse model of iron overload. DFO and DFX together quickened the iron chelation process, although their effectiveness in improving hemograms seemed to be limited. The combination treatment should be considered only for urgent lowering of the iron burden [29].

Sixty-four BTM cases treated with iron chelators and blood transfusions were included in Al-Kuraishy's study. The level of ferritin was assessed using DFX and DFO therapy. According to the data, DFO causes an increase in ferritin concentration when compared to

DFX, indicating that DFX is a more effective treatment for iron overload than DFO [30].

Furthermore, Hasan's findings indicate that DFX was successful in lowering ferritin levels in this group of hemoglobinopathy patients to a level that was consistent with findings from other international research [31].

When compared to patients treated with either DFO or DFX alone, patients treated with combination DFO and DFX had a marked increase in liver enzymes.

Ali's study, which comprised 105 BTM patients treated with DFX and DFO, showed an increase in GOT and GPT in cases of β-thalassemic patients as compared to the control group.

There was no discernible variation in the renal function tests across the three research groups.

Elevations of urea and creatinine have been linked to DFX and DFO. These altitudes are usually modest, though. DFX, individuals who take these medications had higher creatinine concentrations. Urea levels can rise, and some patients have been documented to experience elevated creatinine and urea levels after using DFX [32].

Sanchez-Gonzalez show that DFX enhanced urine protein, albumin and glucose excretion, tubular necrosis/apoptosis, and increased tubular damage after 24h following treatment. The renal tubular cells are directly harmed by DFX treatment, which affects renal function and raises the levels of urea and creatinine [33].

Numerous investigations and reports have demonstrated that the two medications, DFX and DFO, have a real and direct impact on the epithelial cells that line the urinary system and the urinary glomeruli. This could certainly contribute to the kidneys functioning less well and to higher blood levels of urea and creatinine [32].

5. Conclusion

Those treated with DFX had considerably lower serum ferritin levels than those treated with DFO alone or in combination with DFX. While there were no discernible variations in the concentrations of urea and creatinine between the treatment regimens, the liver enzymes of those treated with DFO + DFX were significantly higher.

References

1. H. Bajwa and H. Basit, Thalassemia. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545151/
2. A. F. Chaudhry, Z. Malik, and C. J. Shegos, "Rare co-inherited alpha-thalassemia minor and beta-thalassemia minor with heterozygous H63D mutation mistaken as iron deficiency anemia: a case report," *AME Case Reports*, vol. 6, 2022.
3. A. Makis, E. Voskaridou, I. Papassotiriou, and E. Hatzimichael, "Novel therapeutic advances in β-thalassemia," *Biology (Basel)*, vol. 10, no. 6, p. 546, 2021.
4. S. E. Kababi, B. E. Khalfi, K. E. Maani, and A Soukri, "Beta thalassemia major: overview of molecular etiology, pathophysiology, current and novel therapeutic approaches," *International Blood Research & Reviews*, vol. 10, no. 2, pp. 1–15, 2020.
5. V. Sangkhae and E. Nemeth, "Regulation of the iron homeostatic hormone hepcidin," *Adv. Nutr.*, vol. 8, no. 1, pp. 126–136, 2017.
6. S. Ali, S. Mumtaz, H. A. Shakir, M. Khan, H. M. Tahir, S. Mumtaz, *et al.*, "Current status of beta-thalassemia and its treatment strategies," *Mol. Genet. Genomic. Med.*, vol. 9, no. 12, p. e1788, 2021.
7. J. L. Carson, G. Guyatt, N. M. Heddle, B. J. Grossman, C. S. Cohn, M. K. Fung, *et al.*, "Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage," *Jama*, vol. 316, no. 19, pp. 2025–2035, 2016.
8. S. Mettananda, H. Pathiraja, R. Peiris, N. Wickramarathne, D. Bandara, U. de Silva, *et al.*, "Blood transfusion therapy for β-thalassemia major and hemoglobin E βthalassemia: Adequacy, trends, and determinants in Sri Lanka," *Pediatr. Blood Cancer*, vol. 66, no. 5, p. e27643, 2019.
9. M. Pedram, K. Zandian, B. Keikhaie, R. Akramipour, A. Hashemi, F. Ghahfarokhi, *et al.*, "A report on chelating therapy and patient compliance by determination of serum ferritin levels in 243 thalassemia major patients," *J. Compr. Pediatr.*, vol. 2, no. 2, pp. 65–69, 2010.
10. N. F. Azman, W.-Z. Abdullah, N. Mohamad, R. Bahar, M. F. Johan, R. Diana, *et al.*, "Practice of iron chelation therapy for transfusion-dependent thalassemia in Southeast Asia," *Asian Biomed.*, vol. 10, no. 6, pp. 537–547, 2016.
11. E. Khandros and J. L. Kwiatkowski, "Beta thalassemia: monitoring and new treatment approaches," *Hematol. Clin.*, vol. 33, no. 3, pp. 339–353, 2019.
12. H. M. Moukhadder, R. Halawi, M. D. Cappellini, and A. T. Taher, "Hepatocellular carcinoma as an emerging morbidity in the thalassemia syndromes: a comprehensive review," *Cancer*, vol. 123, no. 5, pp. 751–758, 2017.
13. I. Motta, M. Mancarella, A. Marcon, M. Vicenzi, and M. D. Cappellini, "Management of ageassociated medical complications in patients with β-thalassemia," *Expert Rev. Hematol.*, vol. 13, no. 1, pp. 85–94, 2020.
14. E. A. Rachmilewitz and P. J. Giardina, "How I treat thalassemia," *Blood J. Am. Soc. Hematol.*, vol. 118, no. 13, pp. 3479–3488, 2011.
15. W. Muhammad, M. Ishaq, M. J. Khan, U. Ahmad, and M. Waseem, "Iron chelation therapy needed for serum ferritin overloaded patients of beta thalassemia major," *Thalass Reports*, vol. 11, no. 1, pp. 8–12, 2021.
16. M. Ghanavat, A. F. Varzaneh, and N. Reisi, "The effect of combination iron chelating agents on reducing the severity grading of heart and liver iron overload in βthalassemia patients," *Iran J. Pediatr. Hematol. Oncol.*, vol. 9, no. 4, 2019.
17. H. Dou, Y. Qin, G. Chen, and Y. Zhao, "Effectiveness and safety of deferasirox in thalassemia with iron overload: a meta-analysis," *Acta Haematol.*, vol. 141, no. 1, pp. 32–42, 2019.
18. D. Songdej, N. Sirachainan, P. Wongwerawattanakoon, W. Sasanakul, P. Kadegasem, W. Sungkarat, *et al.*, "Combined chelation therapy with daily oral

deferiprone and twice-weekly subcutaneous infusion of desferrioxamine in children with βthalassemia: 3-year experience," *Acta Haematol.*, vol. 133, no. 2, pp. 226–236, 2015.
19. A. Lal, *et al.*, "Combined chelation therapy with deferasirox and deferoxamine in thalassemia," *Blood Cells Mol. Dis.*, vol. 50, pp. 99–104, 2013. [Google Scholar] [PubMed][Green Version]
20. Y. Aydinok, *et al.*, "Effects of deferasirox-deferoxamine on myocardial and liver iron in patients with severe transfusional iron overload," *Blood*, vol. 125, pp. 3868–3877, 2015. [Google Scholar] [PubMed][Green Version]
21. E. Cassinerio, *et al.*, "Combination of deferasirox and deferoxamine in clinical practice: an alternative scheme of chelation in thalassemia major patients," *Blood Cells Mol. Dis.*, vol. 53, pp. 164–167, 2014. [Google Scholar]
22. N. Arandi, *et al.*, "Combination therapy—Deferasirox and deferoxamine—In thalassemia major patients in emerging countries with limited resources," *Transfus. Med.*, vol. 25, pp. 8–12, 2015. [Google Scholar]
23. A. Eghbali, P. Shokri, R. R. Afzal, and B. Bagheri, "A 1-year randomized trial of deferasirox alone versus deferasirox and deferoxamine combination for the treatment of iron overload in thalassemia major," *Transfus. Apher. Sci.*, vol. 58, pp. 429–433, 2019. [Google Scholar]
24. E. Voskaridou, V. Komninaka, A. Karavas, E. Terpos, V. Akianidis, and D. Christoulas, "Combination therapy of deferasirox and deferoxamine shows significant improvements in markers of iron overload in a patient with β-thalassemia major and severe iron burden," *Transfusion*, vol. 54, pp. 646–649, 2014. [Google Scholar]
25. C. Takpradit, *et al.*, "Using of deferasirox and deferoxamine in refractory iron overload thalassemia," *Pediatr. Int.*, vol. 63, pp. 404–409, 2021. [Google Scholar]
26. W. W. Daniel and C. L. Cross, *Biostatistics: A foundation for analysis in the health sciences*. Wiley, 2018.
27. R. Origa, *et al.*, "Safety and efficacy of the new combination iron chelation regimens in patients with transfusion-dependent thalassemia and severe iron overload," *Journal of Clinical Medicine*, vol. 11, no. 7, 2010. https://doi.org/10.3390/jcm11072010
28. R. J. Ali, D. R. Ali, Z. I. Ahmed, A. A. Ahmed, D. S. Hassen, and R. M. Tahir, "Comparison of deferasirox and deferoxamine effect on liver enzyme activities and ferritin level in patients with beta-thalassemia," *Zanco J. Med. Sci.*, vol. 24, no. 3, pp. 354–359, 2020.
29. D. Wu, X. Wen, W. Liu, H. Hu, B. Ye, and Y. Zhou, "Comparison of the effects of deferasirox, deferoxamine, and combination of deferasirox and deferoxamine on an aplastic anemia mouse model complicated with iron overload," *Drug Des. Devel. Ther.*, pp. 1081–1091, 2018.
30. K. Chatterjee, S. Zaman, R. Chaurasia, S. Singh, S. D. Keil, S. Tewari, *et al.*, "Evaluation of Mirasol pathogen reduction system by artificially contaminating platelet concentrates with Staphylococcus epidermidis: a pilot study from India," *Asian J. Transfus. Sci.*, vol. 10, no. 2, p. 127, 2016.
31. K. H. Hasan, A. Sofijanova, L. Hassan, and N. Al-Allawi, "Deferasirox effect on serum ferritin in Iraq patients with hemoglobinopathies: a single center experience," *Open Access Maced. J. Med. Sci.*, vol. 9, no. B, pp. 144–148, 2021.
32. H. Badeli, A. Baghersalimi, S. Eslami, F. Saadat, A. H. Rad, R. Basavand, *et al.*, "Early kidney damage markers after deferasirox treatment in patients with thalassemia major: a case-control study," *Oxid. Med. Cell Longev.*, vol. 2019, 2019.
33. P. D. Sanchez-Gonzalez, F. J. Lopez-Hernandez, A. I. Morales, J. F. Macias-Nunez, and J. M. LopezNovoa, "Effects of deferasirox on renal function and renal epithelial cell death," *Toxicol. Lett.*, vol. 203, no. 2, pp. 154–161, 2011.