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A Review of Chelating Agents for Iron Overload Treatment

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ABSTRACT

Iron chelation therapy is used to reduce iron overload development due to its deposition in various organs such as the liver and heart after regular transfusion. In this review, different iron chelators implicated in the treatment of iron overload in various clinical conditions have been evaluated using more up-to-date studies focusing on these therapeutic agents. Deferoxamine, Deferiprone and Deferasirox are the most important specific US FDA-approved iron chelators. Each of these chelators has its advantages and disadvantages, various target diseases, levels of deposited iron and clinical symptoms of the afflicted patients which may affect their selection as the best modality. Taken together, in many clinical disorders, choosing a standard chelator does not have an accurate index which requires further clarification. This review aims to introduce and compare the different iron chelators regarding their advantages and disadvantages, usage dose and specific applications.

INTRODUCTION

Iron is one of the essential elements in the body and its concentration is tightly regulated. Iron overload during iron deposition in multiple organs is along with serum ferritin value over 1000 µg/L. Iron overload, either genetically or acquired, may occur due to several conditions such as frequent transfusions, abuse consumption of iron (often as a supplement) and chronic hepatitis have the potential to cause acquired iron overload. Among genetic disorders that cause iron overload including hereditary hemochromatosis (all types), African iron overload, sickle cell disease, major beta-thalassemia, sideroblastic anaemia, enzyme deficiency (pyruvate kinase, G6PD) and rare disorders of transporting proteins (Atransferrinemia, Aceruloplasminemia), hereditary hemochromatosis is the most common genetic causes of iron overload.

Thalassemia is a condition involving a reduction in globin chain (-a or -b) production thus resulting in abnormal haemoglobin which leads to anaemia. Anaemia often needs to be controlled via continuous blood transfusion. This transfusion, coupled with hemolysis of abnormal haemoglobin and increased rate of iron absorption, results in the build-up of iron in the body. If left untreated, the excessive iron level may harm vital organs (liver, heart, and endocrine organs) and manifest as complications of thalassemia. 71% mortality in cardiac disease due to iron accumulation in the myocardium is a significant complication of iron overload in beta-thalassemia. Thus, iron chelators were introduced as drugs capable of bonding with iron, creating an iron-chelator complex that can then be excreted from the body, ultimately reducing the patient's iron load.1 There are currently three available iron chelators: deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP), each with its own benefits and drawbacks. Deferoxamine was the first and most studied iron chelator worldwide, but due to its subcutaneous or intravenous mode of delivery, it has become unpopular with patients. The DFP and DFX are available in oral form, which eases usage and increases adherence (thus increasing the overall survival rate) in thalassemia patients.2 Differences in molecular size of the chelators result in different iron-chelator interactions. Hence, each chelator has its own effectivity and side effects.

DIFFERENT TYPES OF IRON CHELATORS AND REVIEW OF THEIR GENERALITIES

1. DEFEROXAMINE

(DFO or Desferal) is a non-toxic iron chelator that is clinically approved and effective for long-term iron chelation therapy in beta-thalassemia and other iron overload cases. A remarkable effect of DFO on the reduction of serum ferritin levels and hepatic iron is inevitable which increases longevity. Despite DFO oral absorption ability, the pharmacokinetics of oral forms of chelators is not optimal. Ineffectively its intramuscular injection also has been proven. Therefore, it is not used orally or IM and continuous intravenous or subcutaneous infusion should be recommended.

The main mechanisms of iron deposition by DFO are as follows:

1. DFO is a hexadentate chelator, binding iron at a 1:1 molar ratio.
2. Reticuloendothelial system macrophages will release old RBC iron storage, precipitated by DFO, and rapidly excreted through urine.
3. Non-bonded DFO will be internalized by liver parenchymal cells attached to excess hepatic iron and excreted via bile.
4. DFO can directly absorb iron accumulation in cardiac muscle cells.

Due to DFO's short plasma half-life, continuous injection is required for patients with iron overload until iron level disposal reaches to 15 mg daily. As a result of the nocturnal injection of Deferoxamine, 20 to 50 mg of iron (600 to 1,500 mg per month) should be excreted through urine and faeces daily. Therefore, it can minimize iron reaccumulation and decrease its storage if the transfusion is less than 4 packed RBC per month (less than 800 mg of iron). Although the treatment with DFO is effective, its infusions are time-consuming, expensive and painful in children. Moreover, they frequently harm patient's quality of life.

Dose-dependent side effects of Deferoxamine are visual and auditory neurotoxicity due to chronic treatment and acute effects including abdominal pain, diarrhea, nausea, vomiting and hypotension. Accordingly, annual testing by optometrists and audiometerists is recommended.

Fortunately, most toxicity is reversible when DFO treatment is withdrawn. Treatment with high doses of DFO is associated with blood pressure increase in the lungs. Deferoxamine therapy increases the risk of infection of mucormycosis, vibrio and yersinia. It should be mentioned that it cannot be seen with other iron chelators such as Deferasirox and Deferiprone because they do not work as siderophores.

2. DEFERASIROX

Tridentate iron chelating agent that binds iron in a 2:1 ratio. This combination has a high affinity for iron and a very low affinity for copper and zinc. The most common side effects of DFX are abdominal pain, nausea, vomiting, diarrhoea, skin rashes and ophthalmic complications. These reactions frequently occur in older patients with a predisposition to myelodysplastic syndrome, renal or hepatic disease and patients with low platelet counts. Serum creatinine level, serum transaminases, bilirubin and CBC should be regularly monitored. One of the troublesome factors in Deferasirox therapy is proximal renal tubular dysfunction and other complications including drastic levels of metabolic acidosis, hypophosphatemia and hypokalemia.

In study from Al-Khabori, et al. Deferasirox withdrawal and replacement therapy in 4 patients with similar conditions rapidly resulted in a normal balance of electrolytes. It is worth noting that to prevent these complications; patients should avoid the use of antacid-containing aluminium such as Maalox and Mylanta during Deferasirox therapy.

3. DEFERIPRONE

Oral iron chelator which is a proper choice for patients who showed an inadequate response to prior chelation therapy such as Deferasirox and Deferoxamine. The most typical side effects include elevated liver enzymes, gastrointestinal disorders and arthralgia. The most serious adverse effects associated with DFP are agranulocytosis and neutropenia with an incidence of 0.2 and 2.8 per 100 patients over one year that are reversible after stopping therapy.

A major problem in Deferiprone therapy in hepatic cell culture studies (with iron accumulation) demonstrated that increased oxidative DNA damage occurs when the chelator

ratio is lower than iron concentration. The primary recommended oral dose of Deferiprone is 25 mg/kg 3 times a day (daily consumption: 75 mg/kg) and the maximum recommended daily use is 100 mg/kg. For agranulocytosis and neutropenia monitoring during therapy, neutrophil absolute count should be performed regularly. In comparison with Deferoxamine and Deferasirox, it seems that Deferiprone is not successful enough in controlling iron overload in thalassemia. Despite its high per cent (79%-80%) acceptance compared to deferoxamine (59%-78%), its efficiency and immunity remain questionable. Deferiprone is used as the second choice treatment in major beta-thalassemia patients when deferoxamine is not available.

Basically, in iron overload conditions such as hereditary hemochromatosis, deferiprone therapy would be intolerable. Also, transfusion-dependent patients with severe conflict cardiac require more serious chelation therapy than regular patients with chelation therapy. In such cases, combination therapy with subcutaneous or intravenous deferoxamine and oral deferiprone is recommended. This combination therapy will significantly improve severe cardiac siderosis or left ventricular dysfunction.

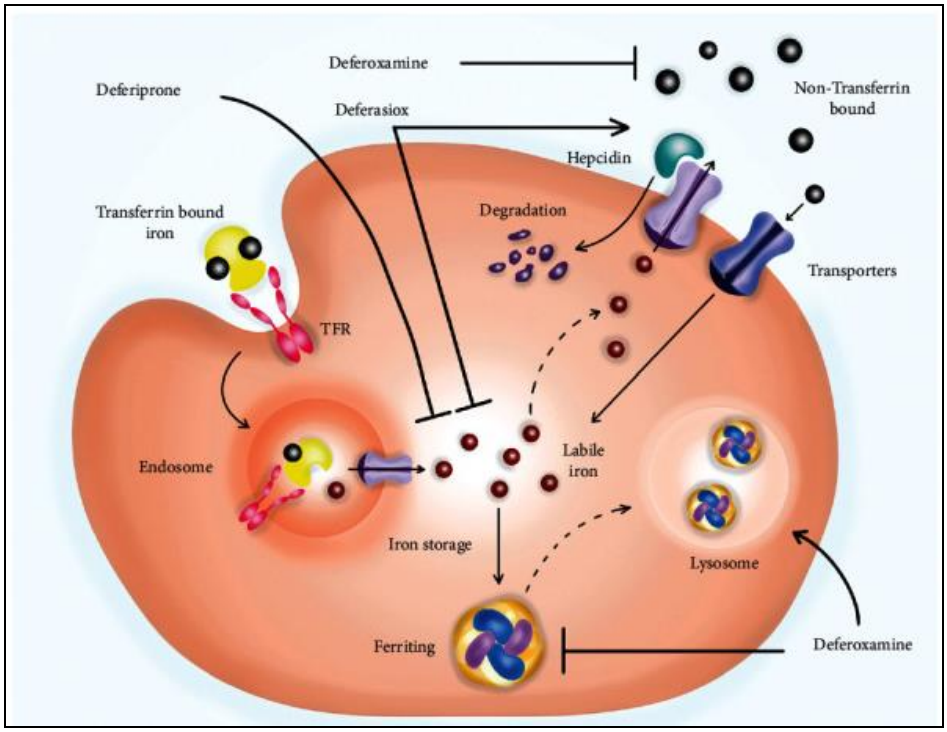

Fig 1 Deferoxamine, deferiprone, and deferasirox mechanism of action in the management of iron overload. Deferoxamine binds to nontransferrin bound iron or to iron found in ferritin

forming a molecule which is later excreted via the kidneys. Deferoxamine also promotes ferritin degradation in lysosomes. Deferiprone and deferasirox chelate cytosolic labile iron. Besides, deferasirox can increase the levels of hepcidin that results in the degradation of ferroportin. TFR, transferrin receptor.

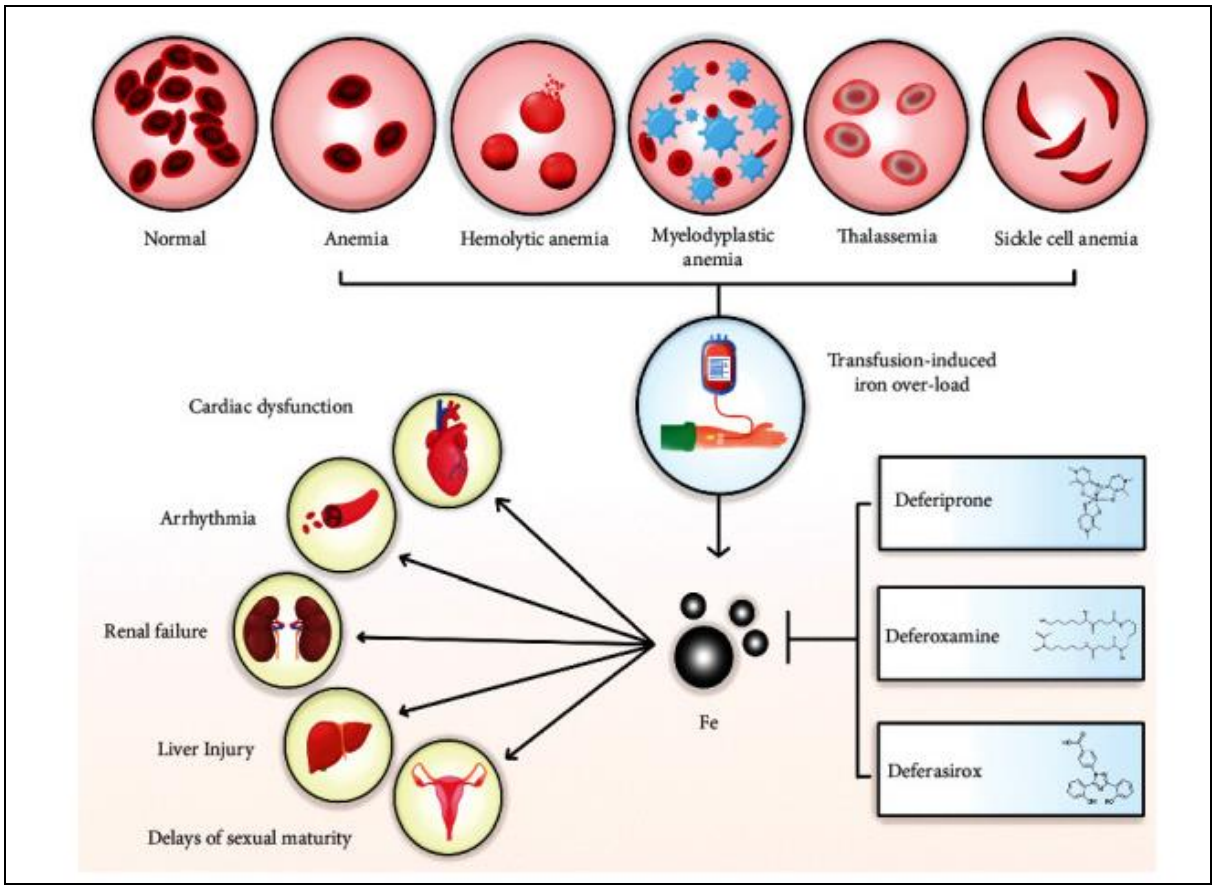

Fig 2 Deferoxamine, deferiprone, and deferasirox effects on transfusion-induced iron overload. Patients with aplastic anemia, hemolytic anemia, myelodysplastic anemia, thalassemia, and sickle cell anemia become transfusion-dependent. Iron toxicity leads to free radical production, which causes severe side effects, including cardiac dysfunction, arrhythmia, renal failure, kidney damage, and delays in sexual maturity. Iron chelators can enter cells, bind free iron, and remove it from the body, thus inhibiting iron toxicity.

TABLE 1 COMPARISON OF GENERAL PROPERTIES OF IRON CHELATORS

PROPERTY	DEFEROXAMINE	DEFERASIROX	DEFERIPRONE
Route	Subcutaneous, Intravenous	Oral	Oral
Usual Dose	25-50 Mg/Kg/Day	20-30 Mg/Kg/Day	75 Mg/Kg/Day
Schedule	Day Over 8-24 Hours, 5 Days Per Week	Once A Day	In 3 Divided Doses Daily
Sid Effect	Rash, Ophthalmological, Auditory	Gastrointestinal, Renal Failure	Gastrointestinal, Agranulocytosis/ Neutropenia, Arthralgia
Advantage	Availability Of Information	Oral And Daily Use	Effective In Cardiac Iron Excretion
Disadvantage	Significant Toxicity	Unavailability Of Complete Information	Blood Count Monitoring

ADVANTAGES

- Chelation therapy aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and or faces with chelators. If chelation has been delayed or has been inadequate, it will be necessary to excrete iron at a rate that exceeds this.
- Recognized first-line treatment in iron overload
- Long-term experience and data
- reduced morbidity and mortality
- Effective in maintaining near-normal iron stores
- Specific affinity for iron with high chelating efficiency
- Achieves negative iron balance
- Reversal of cardiac disease with intensive therapy

LIMITATIONS

- Requires maximum exposure for optimal outcome
- Not absorbed from the GI tract
- Rapidly eliminated
- 30-minute half-life requires prolonged infusions
- Requires parenteral infusion

TABLE 2 COMPARISON OF THE PHYSICOCHEMICAL PROPERTIES OF IRON CHELATORS

PROPERTY	DEFEROXAMINE	DEFERASIROX	DEFERIPRONE
Molecular Weight	560	373	139
Chelator: Iron Ratio In Complex	1:1 (Hexadentate)	2:1 (Tridentate)	3:1 (Bidentate)
Lipid Solubility	Low	High	Medium
Route Of Administration	Subcutaneous Or Intravenous	Oral	Oral
Iron Excretion	Urinary And Fecal	Faecal	Urinary
Plasma Half-Life	20 Min	12-16 Hr	1-4 Hr
Usual Treatment (Mg/Kg/Day)	40	20-40	75-100 (Divided Into Three Doses)
Licensed	For Treatment Of Chronic Iron Overload Resulting From Transfusion-Dependent Patients With Anaemia	In The U.S., For Treatment Of TM (Age, 22 Yr); In Europe, For Treatment Of TM (Age, 26 Yr, When Deferoxamine Is Contraindicated Or Inadequate)	For Treatment Of Iron Overload In TM When Deferoxamine Is Contraindicated Or Inadequate
TIF Guidelines	Age, >2 Yr. First-Line Treatment Line Treatment	Age, 2-6 Yr: Insufficient Data; Age, >6 Yr: Second-Age, 2-6 Yr. First-Line Treatment In The U.S., Second-Line Age, >2 Yr. First-Line Treatment Line Treatment	Age, 2-6 Yr: Insufficient Data; Age, >6 Yr: Second-Age, 2-6 Yr. First-Line Treatment In The U.S., Second-Line
Cost For A Patient With A 63-Kg Body	£5,584, Or $7,148 (5 Days/Wk; 90 Mg/Kg)	£23,179, Or $29,669 (7 Days/Wk; 30 Mg/Kg)	£5,519, Or $7,064 (7 Days/Wk; 75 Mg/Kg)
Cardiac Iron	Improvement In T2-Weighted MRI, But	Improvement In T2-Weighted MRI With	The Most Effective Of The Three

	Adherence Problems, Not Effective In All Patients; Continuous IV Administration Ameliorates Cardiac Dysfunction; Effective In Combination With Deferiprone And Deferasirox	Monotherapy Or In Combination With Deferoxamine	Chelators; Improvement- Ment In T2-Weighted MRI With Monotherapy
Liver Iron	Reduction In Liver Iron And Amelioration Of Liver Abnormalities	Reduction In Liver Iron And Amelioration Of Liver Abnormalities	Equivalent To Deferoxamine For Reducing Liver Iron
Main Side Effects	Reactions At The Infusion Site, Auditory And Retinal Toxic Effects, Allergy, Bone Abnormalities, Yersinia Infection	Gastrointestinal Symptoms, Rashes, Adverse Renal Effects	Gastrointestinal Symptoms, Neutropenia, Agranulocytosis, Arthralgia, Elevated Liver-Enzyme Levels, Zinc Deficiency In Patients With Diabetes

FUTURE SCOPES

Various studies have shown the safety and efficiency of chelation therapy in the treatment of iron overload in major beta-thalassemia patients with chronic transfusion. Since the transfusion volume affects the chelation dosage, monitoring iron intake is necessary, especially in children.

Using iron chelation therapy in transfusion-dependent anaemia such as MDS, aplastic anaemia and sickle cell disease has been approved. Recent reviews indicate that therapy response depends on chelation dosage and iron overload in the body.

Various studies on the effect of iron overload due to transfusion in patients with different types of rare anaemia have shown that doses of DXM and regular monitoring of serum ferritin levels are the factors involved in the control of iron.

CONCLUSION

Several conditions including severity of iron overload, treatment period, final costs of treatment and the results of recent studies must be taken into consideration to select the

proper chelation therapy for a particular clinical situation. Furthermore, the additional expenses of treatment and the cost of medications should be considered. Iron is also an important element in the proliferation of tumour cells. Hence, in the absence of this vital element, the proliferation of malignant cells will be also difficult. Therefore, shortly, the potential role of chelation therapy in the treatment and control of cancers will be considered.

REFERENCES

1. Angelucci E. Another Step Forward in Iron Chelation Therapy. Acta Haematol. 2015;134(4):231–2.
2. Leitch HA. Hematologic improvement with Iron chelation therapy in acquired anaemias. Eur J Haematol. 2016;96(6):551–2.
3. Kontoghiorghe CN, Kontoghiorghes GJ. New developments and controversies in iron metabolism and iron chelation therapy. World J Methodol. 2016;6(1):1–19.
4. Poggiali E, Cassinerio E, Zanaboni L, et al. An update on iron chelation therapy. Blood Transfus. 2012;10(4):411–22
5. Ghorban K, Shanaki M, Mobarra N, et al. Apolipoproteins A1, B, and other prognostic biochemical cardiovascular risk factors in patients with beta-thalassemia major. Hematology. Hematology. 2016;21(2):113–20
6. Fedele R, Cuzzola M, Irrera G, et al. Polycythemia following allogeneic hematopoietic progenitor cell transplantation occurs during iron chelation therapy. Leuk Lymphoma. 2016;57(4):969–72.
7. Diamantidis MD, Neokleous N, Agapidou A, et al. Iron chelation therapy of transfusion-dependent beta-thalassemia during pregnancy in the era of novel drugs: is deferasirox toxic? Int J Hematol. 2016;103(5):537–44.
8. Efficace F, Santini V, La Nasa G, et al. Health-related quality of life in transfusion-dependent patients with myelodysplastic syndromes: a prospective study to assess the impact of iron chelation therapy. BMJ Support Palliat Care. 2016;6(1):80–88
9. Salgia RJ, Brown K. Diagnosis and management of hereditary hemochromatosis. Clin Liver Dis. 2015;19(1):187–98
10. Altes A, Sanz C, Bruguera M. Hereditary hemochromatosis. Problems in diagnosis and treatment. Medicina Clinica. 2015;144(9):424–8.
11. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. Br J Haematol 2016;172:512-23.
12. 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;89:1187-93.
13. Propper RD, Nathan DG, Cooper B, Rufo RR, Nienhuis AW, Anderson DF. Continuous subcutaneous (SC) infusion of desferrioxamine (DF) in patients with iron (Fe) overload. Blood 1976;48:964. abstract.
14. Propper RD, Cooper B, Rufo RR, et al. Continuous subcutaneous administration of deferoxamine in patients with iron overload. N Engl J Med 1977;297:418-23.
15. Hussain MAM, Green N, Flynn DM, Hussein S, Hoffbrand AV. Subcutaneous infusion and intramuscular injection of desferrioxamine in patients with transfusional iron overload. Lancet 1976;2:1278- 80.
16. Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet 2000;355:2051-2.
17. Hider RC, Kontoghiorghes G, Silver J. Pharmaceutical compositions: UK Patent GB2118176, 1983 (Priority date 1982).
18. Gyparaki M, Porter JB, Hirani S, Streater M, Hider RC, Huehns ER. In vivo evaluation of hydroxypyridone iron chelators in a mouse model. Acta Haematol 1987;78:217-21.
19. Porter JB, Gyparaki M, Burke LC, et al. Iron mobilization from hepatocyte monolayer cultures by chelators: the importance of membrane permeability and the iron-binding constant. Blood 1988;72: 1497-503.
20. Porter JB, Morgan J, Hoyes KP, Burke LC, Huehns ER, Hider RC. Relative oral efficacy and acute toxicity of hydroxypyridin-4-one iron chelators in mice. Blood 1990;76:2389-96.

21. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood. 1997;89:739-61.
22. Cappellini MD, Bejaoui M, Agaoglu L, Porter J, Coates T, Jeng M, et al. Prospective evaluation of patient-reported outcomes during treatment with deferasirox or deferoxamine for iron overload in patients with b-thalassemia. Clin Ther. 2007;29:909-17.
23. Kontoghiorghe CN, Kontoghiorghes GJ. New developments and controversies in iron metabolism and iron chelation therapy.World J Methodol. 2016;6:1-19.
24. Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. Br J Haematol. 2002;118:330-6.
25. Chand G, Chowdhury V, Manchanda A, Singh S. Deferiproneinduced arthropathy in thalassemia: MRI findings in a case. Indian J Radiol Imaging. 2009;19:155-7.
26. Choudhry V, Pati H, Saxena A, Malaviya A. Deferiprone, efficacy and safety. Indian J Pediatr. 2004;71:213-6.
27. Cohen A, Galanello R, Piga A, Vullo C, Tricta F. A multi-centre safety trial of the oral iron chelator deferiprone. Ann N Y Acad Sci. 1998;850:223-6.
28. Ha SY, Chik KW, Ling SC, Lee AC, Luk CW, Lam CW, et al. A randomized controlled study evaluating the safety and efficacy of deferiprone treatment in thalassemia major patients from Hong Kong. Hemoglobin. 2006;30:263-74.
29. Hoffbrand AV, Al-Refaie F, Davis B, Siritanakatkul N, Jackson BF, Cochrane J, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood. 1998;91:295-300.
30. Naithani R, Chandra J, Sharma S. Safety of oral iron chelator deferiprone in young thalassaemics. Eur J Haematol. 2005;74:217-20. 11. Tewari S, Tewari S, S
31. Origa R., Piga A., Tartaglione I., et al. Renal safety under long-course deferasirox therapy in iron overloaded transfusion-dependent β-thalassemia and other anemias. American Journal of Hematology . 2018;93(7):E172–E175. doi: 10.1002/ajh.25122
32.Poggiali E., Cassinerio E., Zanaboni L., Cappellini M. D. An update on iron chelation therapy. Blood Transfusion = Trasfusione del Sangue . 2012;10(4):411–22. doi: 10.2450/2012.0008-12.