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Clinical Pharmacology and Toxicology of the Current and New Potential Therapeutic Agents for the Treatment of Iron Overload

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Review Article

ABSTRACT

Iron poisoning has been linked to morbidity and mortality due to iron overdose or chronic iron deposition in the body. It is a big challenge to treat the iron overload associated diseases including hemochromatosis, thalassemia and sideroblastic anemias. Although, therapeutic phlebotomy is still the cornerstone therapy in the patients with hereditary hemochromatosis and other blood disorders, yet chelation therapy is currently used and is in the continuous process of development for the patients with iron overload associated diseases. Patients requiring transfusions over lifetime have iron accumulation in multiple organ systems including liver, heart and endocrine system, which could ultimately lead to organ failure. Therefore, iron-chelation is a necessary step to prevent organ failure and reduce mortality resulting from an acute or chronic iron poisoning. The availability of the wide variety of chelating agents in the market makes the treatment of iron poisoning more challenging and socioeconomic problem in healthcare. Recently, the clinical studies on existing and new chelating agents have been expanded considerably to include disorders associated with iron overload or diseases in which the iron plays a key role in the pathophysiology. Since, last several years there is an increase in the unapproved over the counter (OTC) chelation products marketed with claims to prevent or treat diseases. The US Food and Drug Administration (FDA) has raised concern over the use of several unapproved OTC chelation products, and has issued warnings against unproven claims of these chelation therapies. The current review presents the clinical pharmacology, clinical indications and toxicity of the recommended iron-chelating agents such as deferoxamine, deferiprone, and deferasirox for the treatment of iron overload. The recent advances in finding the new chelating agents including the desferrithiocin derivative and currently available calcium channel blockers undergoing the clinical trials for the treatment of iron overload are also discussed.

INTRODUCTION

Iron overdose has been the problem since last several years, resulting from either the chronic blood transfusion in the patients with disorders, including sickle cell disease, thalassemia, and myelodysplastic syndromes, or due to the ingestion of excess iron from the drug sources including vitamins and supplements. When left untreated, the iron overload could cause significant adverse effects on multiple organ systems including liver, heart, brain, and endocrine system with the pathophysiology of cardiomyopathy, diabetes, liver dysfunction, and acceleration of various neurodegenerative diseases [1-3].

Therapeutic phlebotomy is also referred to as venesection or bloodletting, and is currently recommended for the treatment

of polycythemia vera, secondary polycythemias, hemochromatosis and porphyria cutanea tarda [4,5]. Although therapeutic phlebotomy remains the treatment of choice for the above-mentioned conditions, there are other options available. The automated therapeutic erythrocytapheresis selectively removes red blood cells and recent data from human studies revealed that it could be a potentially effective treatment option for patients with hereditary hemochromatosis exhibiting intolerance to phlebotomy [6,7]. The chelating agents also provide a potential method of treating metal toxicity, thus, minimizing the adverse events associated with toxicity of iron. Chelation therapy has come a long way, yet it is the most controversial and misappropriated intervention in clinical toxicology [8]. According to Federal Drug Association (FDA), all chelation therapy products require an approved prescription and should be used under the supervision of a healthcare practitioner. However, there are multiple unapproved chelating agents available in the market, sold with the claim to have the capability to get rid of the metal toxicity. FDA has identified concerns with chelating agents that are available as dietary supplements in various formulations including suppositories, nasal sprays, clay bath, and liquid drops. Additional concern of FDA applies to the unapproved tests claimed by some companies that are marketing over-the-counter (OTC) products, to provide the chelation therapy for the detection of presence of metals in urine. These unauthorized companies market OTC chelation agents that are commonly targeting patients with diseases such as autism, Alzheimer's, Parkinson's, diabetes, cardiovascular conditions, and other health conditions with narrow treatment possibilities. Thus, FDA has repeatedly raised concerns and issued several warnings to the companies marketing OTC chelation products with no proven safety and efficacy studies to prevent or treat diseases [9]. The present review provides a current update of the iron overload treatment including therapeutic phlebotomy and FDA approved iron-chelating agents such as deferoxamine, deferiprone, and deferasirox for the acute iron poisoning and chronic iron overload. It also summarizes briefly the recent advances in potential new drug development against iron overload.

Iron Overload and Therapeutic Phlebotomy

Therapeutic phlebotomy is currently recommended for treatment of the blood disorders in which red blood cells (RBCs) or serum iron removal manages disease symptoms and complications as in the symptomatic and asymptomatic patients of hereditary hemochromatosis. The two steps of therapeutic phlebotomy includes an initial induction step to induce iron depletion followed by maintenance step to prevent excess iron re-accumulation [10]. In the patients with absolute polycythemia including polycythemia vera and secondary polycythemia, the treatment goals are different. In polycythemia vera, the overall goal is to reduce the RBCs and serum iron together with the beneficial therapeutic reduction of white blood cells and platelets. However, in porphyria cutaneous tarda, the preferred therapy is to remove iron by phlebotomy until the enzyme uroporphyrinogen decarboxylase activity is resumed [11]. Recent study on children with sickle cell anemia, stroke and transfusional iron overload revealed the safety and efficacy of the therapeutic phlebotomy [12].

Toxicity

Assi and Baz have reported some limitations including intolerance or low acceptance of therapeutic phlebotomy in some patients [5]. There were no absolute contraindications reported by these researchers, however the relative contraindications including severe heart disease and anemia were reported. The frequent phlebotomy results in fatigue, dizziness and rarely iron deficiency [5].

Iron Toxicity and Chelation Therapy

Iron toxicity may result in significant morbidity, ultimately leading to mortality around the world. Iron is an essential trace element with high reactivity and iron homeostasis is a complex system, therefore, it is absolutely essential to have the balance for the intestinal iron absorption and release of stored iron. Under normal physiological conditions, iron performs a number of functions including carrying and storing oxygen by binding to hemoglobin or myoglobin, catalyzing the redox reactions, and transporting in the cells through the proteins such as transferrin. The concern with human body lacking any regulated mechanism to excrete iron remains, as it leads to chronic iron overload in patients with blood transfusions to treat wide array of hematological disorders such as sickle cell anemia, thalassemia, aplastic anemia, myelodysplastic and myelofibrosis syndromes. Iron-chelation therapy is intended to combat iron overload, as the chelating agents form a complex with iron and promotes its excretion. The need of the transfusion-dependent patient treatment with iron chelating agents is vital, as the iron overload has pathological effect in heart, liver, brain and endocrine system. Regarding the iron toxicity in brain, the growing body of data supports the view that disruption of the cerebral iron regulation plays an important role in the etiology of neurological disorders including Alzheimer's disease and Parkinson's disease [3].

Iron overdose is one of the leading causes of death in both young and adult population. The wide availability of iron as a dietary constituent of multivitamins and supplements provides easy access to both children and adults, thus enhancing the risk for adverse events. The iron-chelation therapy can decrease and in many cases eliminate the morbidity and mortality rates associated with iron toxicity.

Acute Iron Poisoning

Deferoxamine

The treatment approaches of an acute iron toxicity in patients involve optimizing hemodynamic status and providing adequate management care, along with the chelation therapy of deferoxamine [13]. Deferoxamine as the first recommended iron-chelating agent was introduced in the healthcare system but faced significant challenges due to its parenteral use resulting in hypersensitivity and non-compliance. Previous animal studies suggest that deferoxamine is also effective in chelating heavy metals including aluminum, bismuth, and cadmium besides decreasing the absorption of iron [14-17]. The limited literature, however, supports the efficacy of deferoxamine for acute iron toxicity in patients with or without the gastrointestinal decontamination and hemodialysis [18,19]. The earlier human studies on the efficacy of deferoxamine suggested that while it prevents absorption of iron, on the contrary it may exhibit toxicity through a toxic metabolite, ferrioxamine mediated production and absorption [17,20,21]. Currently, deferoxamine is clinically indicated for the acute iron toxicity as an adjunct therapy to the standard measures, including the gastrointestinal decontamination and hemodialysis [19].

Deferiprone

Studies related to the efficacy of deferiprone against acute iron intoxication data in the prevention of iron absorption are limited to the experimental animals. The data from some of the previous studies in animals have shown that deferiprone when given immediately after the iron intoxication, produced a significant decrease in the serum iron levels by increasing iron excretion in feces, and thereby, reducing the mortality in the treatment group, especially in the experimental animals that received a follow up dose of deferiprone [22-24]. A combination therapy of deferasirox and deferiprone in rats exhibited chelation of cadmium and iron [14]. So far, no human studies have been reported that address its usage in the short-term acute iron intoxication.

Chronic Iron Overload

Deferoxamine

Clinical pharmacology: FDA approved Deferoxamine (also known as desferrioxamine or desferal) in 1968 for the treatment of chronic iron overload. Deferoxamine has a short half-life of 5-10 minutes and should be administered parenterally [25]. Deferoxamine is a hexadentate hydrophilic chelating agent forming a stable complex with the molecule of iron in 1:1 ratio [26]. It readily chelates iron from liver, from the proteins such as ferritin and hemosiderin, thereby forming a stable complex, thus preventing iron from entering into Haber-Weiss reaction. Deferoxamine, after metabolism by plasma enzymes, is readily soluble in water and excreted from the body via urine and feces [27].

Clinical use: Long-term clinical studies support deferoxamine as a chelating agent in chronic iron overload with a reduction in liver iron concentration [28]. Deferoxamine has been shown to improve the survival rate in thalassemia patients by attenuating organ system toxicity [29,30]. The reduction in the mortality and incidence of cardiac complications in transfusion dependent patients with thalassemia has demonstrated the beneficial aspect of deferoxamine [29,31,32]. Deferoxamine is also effective for the reversal of the hepatic iron overload by decreasing the liver iron stores and preventing hepatic fibrosis [33]. In sickle cell anemia, deferoxamine administration has been shown to be effective in decreasing the liver iron level in patients [34,35].

Toxicity: The patients administered with deferoxamine should be regularly monitored for kidney function. FDA has issued dose-related warnings that have been reported in post-marketing surveillance, including increase in serum creatinine, renal tubular disorders and acute renal failure. The reported adverse reactions for deferoxamine include hepatic dysfunction, ocular toxicity, auditory toxicity, bone abnormalities, and acute respiratory distress syndrome in different categories of patients treated with deferoxamine [36-39].

Deferiprone

Clinical Pharmacology

In USA, FDA approved Deferiprone in 2011 as the second-line oral iron-chelating agent for the treatment of patients with blood transfusions-induced iron overload, mainly because of conditions such as thalassemia, when the prior or existing chelation therapy is not adequate [40-42]. It has been clinically observed that there is a significant reduction not only in morbidity but also in mortality with the deferiprone and combination therapy with deferoxamine against iron overload in thalassemia patients [43,44]. Deferiprone is a bidentate hydrophilic chelator and forms a stable complex with the molecule of iron in 3:1 ratio that increases iron excretion and concomitantly decreases iron absorption. It is rapidly absorbed and metabolized by the process of glucuronidation in the liver with relatively short half-life of 47-134 minutes [26,45,46]. A recent meta-analysis study revealed a greater urinary iron excretion in patients with iron overload that were given the combination therapy of deferoxamine and deferiprone when compared with patients receiving either of the two drugs alone [47].

Clinical use: FDA has granted an approval of deferiprone treatment to the patients who exhibit iron overload induced by transfusion, due to condition such as thalassemia when current chelation therapy is not sufficient to treat the iron overload. Thalassemia is a serious condition with the risk of developing diabetes, liver disease, heart failure, and arthritis, which can prove fatal. The data from previously conducted trials after prospectively planned analysis revealed that patients did not respond with the deferoxamine therapy, however, treatment of patients with deferiprone revealed it to be a safe and effective chelation therapy as observed with the decrease in serum ferritin levels, thus leading to its approval in the US [17]. Deferiprone in pediatric and adult population of

patients has shown to decrease serum ferritin concentrations in multiple retrospective and observational studies [48-51].

In the patients with sickle cell disorders, myelodysplastic syndrome and the chronic anemia's, the deferiprone safety and efficacy against iron overload have not been evaluated and therefore, deferiprone is not approved by FDA for use in any of these conditions. [52].

Toxicity: The patients should be regularly monitored for the white blood cell counts. The adverse effects associated with deferiprone includes elevated hepatic enzymes, neutropenia, agranulocytosis, arthralgia, and gastrointestinal side effects [53]. The most serious common side effects are agranulocytosis and neutropenia [54,55]. The common gastrointestinal symptoms include nausea, vomiting, and abdominal pain [2,56]. The deferiprone treatment lead to elevation of liver transaminases and has been suggested to cause progressive liver fibrosis in one trial [57]. The other conditions such as arthritis and arthralgia associated with deferiprone have been commonly found to affect the knees as the large joints [58,59].

Deferasirox

Clinical Pharmacology

In 2005, deferasirox was approved by the FDA as the oral suspension formulation for the treatment of chronic iron overload due to blood transfusion dependent hemosiderosis and non-transfusion dependent thalassemia in children and adults. Currently, deferasirox is also formulated as a tablet allowing convenient mode of administration for both adult and pediatric patients [60]. Deferasirox is a non-chiral tridentate lipophilic chelator and forms a complex with molecule of iron in the ratio of 2:1. It is a highly specific chelator of iron and does not induce excretion of zinc or copper [61].

The pharmacokinetic profile of deferasirox has been evaluated following a single or the repeated dose regimen in patients with iron overload as well as healthy volunteers, to attain steady state that was reached after 3 days of treatment [62]. In humans, the deferasirox has low tissue distribution with the half-life of 19+/-6.5 hours at 20 and 40 mg/kg body weight [26,63]. The data from *in vitro* studies have revealed that deferasirox binds to plasma proteins (~ 99%), have strong affinity to serum albumin, and get distributed principally in the plasma [64]. The principal metabolic pathway of deferasirox is through glucuronidation, predominantly by the enzymes including uridine diphosphate glucuronosyltransferase (UGT1) A1 with a minor extent of metabolism by the enzyme UGT1A3. Cytochrome P450 enzymes has a small contribution in catalyzing the hepatic metabolism of the elimination of deferasirox from the body, with observed major excretion in feces (84%) and minor renal excretion as feces (8%) [65].

Clinical use: Deferasirox efficacy has been established in decreasing serum ferritin levels and overall iron overload while demonstrating its efficiency with regard to the liver iron removal [28,66,67]. The excretion of iron as observed by the lowering of the liver iron concentration and serum ferritin, occurred at the higher dose of 20-30 mg/kg day that confirmed its equivalence to deferoxamine in iron overloaded thalassemia patients [28,62,68]. In some patients, the inadequate reduction in liver iron concentration at higher doses may be due to the lack of treatment adherence by patients or an individual variability in drug exposure [22]. Initial data from the animal studies suggest that deferasirox, besides chelating cardiac iron, also possesses the property of gaining access to intracellular iron in a way similar to the other oral chelating agent deferiprone [69,70]. Prior studies have shown the effectiveness of deferasirox in down-regulating the accumulation of cardiac iron in moderate to excessive overload [67,71-78].

Toxicity: Deferasirox therapy also requires close monitoring of the patients that could be attained by the measurement of serum transaminases, bilirubin, creatinine clearance, serum creatinine, and bilirubin. The toxicity of deferasirox includes gastrointestinal side effects such as vomiting, nausea, and abdominal pain along with skin rash, rise in creatinine, elevated hepatic enzymes, renal impairment, gastrointestinal hemorrhage, and hepatic failure. Elderly population and patients with health issues such as high-risk myelodysplastic syndromes, low platelet counts, underlying hepatic or renal impairment have more frequency of the above-defined adverse reactions [28,42,62,68,72,79-81].

Recent Advances in Potential Iron Chelating Agents

Deferitazole

A polyether derivative of desferrithiocin, deferitazole with goal of daily oral administration is currently under non-clinical development for iron overload in patients with transfusion. The inability to draw conclusions from the clinical data led to the termination or withdrawal of its clinical trials. Deferitazole is a tridentate chelator with three dissociation constant, p*k*a: 1.72, 3.78 and 10.70, and forms two different complexes with one and two molecules of iron as deferitazole: Iron in the ratio of 1:1 and 1:2 [82]. The half-life of deferitazole is reported to be 16.2-21.3 h and its acronyms including FBS0701, SSP-004184, and SPD602 are currently in non-clinical drug development [83].

Clinical use: Deferitazole is currently in nonclinical drug development phase, with the termination or withdrawal of the clinical trials due to the inability of being able to draw conclusions from the data and evaluation of ongoing non clinical rat studies [84]. The purpose of clinical studies was to evaluate deferitazole for the treatment of transfusion dependent chronic iron overload in patients with hereditary and acquired anemias and thalassemia [85].

Calcium Channel Blockers Effect on Myocardial Iron Overload in Patients with Thalassemia

Iron-overload in patients with transfusion dependent thalassemia can lead to iron accumulation in heart, leading to iron-overload cardiomyopathy [86]. Previous *in vivo* and *in vitro* studies showed the major pathway for the iron entry is through the L-type calcium channels [87,88].

Amlodipine

Amlodipine has shown no serious adverse effects in clinical study with thalassemia major patients, when administered in addition with current chelation therapy to evaluate the reduction in myocardial iron overload when compared to placebo. Fernandes et al. has shown in thalassemia major patients with cardiac siderosis that the amlodipine treatment in combination with existing chelation therapy has reduced the cardiac iron more efficiently when compared with the patients receiving only the chelation therapy [89,90].

Nifedipine

Nifedipine has currently completed the phase 1 trial for the evaluation of its potential to increase urinary iron excretion among patients with iron overload. Earlier animal studies showed that nifedipine mobilizes iron from the liver with primary and secondary iron overload and enhances urinary iron excretion [91]. Further studies and clinical trials are needed to re-evaluate the efficacy of nifedipine in treating the iron overload.

CONCLUSION

Throughout the world acute iron poisoning poses a significant health problem, which if untreated or with ineffective treatment could result in morbidity and sometimes mortality. Excess iron from the body could be therapeutically removed either by phlebotomy or chelation therapy. Therapeutic phlebotomy is recommended for the patients with excess body iron, tolerance and sufficient hemoglobin. Therapeutic phlebotomy is specially used for the treatment of hereditary hemochromatosis. However, it could become fatal in the patients with transfusional induced iron overload.

The treatment strategies of acute iron poisoning are focused on providing the recommended chelation therapy along with the required supportive care. The classical approach to treat acute iron toxicity involve the use of approved chelating agents along with the adequate patient care while optimizing the hemodynamic status in patients. Deferoxamine was originally recommended for acute iron poisoning, and later was approved for the thalassemia patients with iron overload. The oral treatment of deferoxamine is not possible, due to its poor absorption and short half- life. Deferiprone on the other hand is the oral drug of choice in patients with transfusional induced iron-overload due to thalassemia syndromes, when current chelation therapy is insufficient. In regard with combinational therapy, deferoxamine and deferiprone are recommended for the treatment of iron overload due to thalassemia. Deferasirox is the second oral agent that is recommended for the patients that have intolerance for deferoxamine, deferiprone or combination therapy. Patients with chronic iron overload due to blood transfusions dependent red cell disorders and myelodysplastic syndrome lack the mechanism that could efficiently remove excess iron from the body. Patients requiring transfusions over lifetime also have iron accumulation in multiple organ systems including liver, heart and endocrine system, ultimately leading to organ failure with the enhancement in neurodegenerative disorders in the susceptible patients. Therefore, iron-chelation is a necessary step to prevent organ failure and reduce mortality resulting from an acute or chronic iron poisoning. The oral iron-chelators however, have not been widely studied in humans for an acute iron poisoning and therefore are not approved by FDA for the treatment of acute iron poisoning. The process of iron overload is a chronic and significant socioeconomic and healthcare burden. The parenteral and oral iron-chelating agents including deferoxamine, deferiprone and deferasirox, are recommended and approved by FDA for patients with transfusion dependent red blood cell and other disorders in different case scenarios. The monotherapy is not effective in all patients for a variety of reasons, while the combination therapy may be effective in many situations. There is good prognosis as far as patients with transfusion-induced iron overload are concerned; with well-controlled iron concentration through chelation of iron is concerned. Therefore, patients should avoid OTC chelation therapies with unproven effectiveness and safety that are prominently marketed via Internet or available OTC with claims to reduce the essential or heavy metal concentration in the body.

Few years back, the only chelating agent available was deferoxamine. However, deferoxamine therapy has revealed the undesirable adverse effects along with the issues such as discomfort, pain and hypersensitivity, resulting in its non-compliance. With the emergence of new oral therapies including deferiprone and deferasirox over the last few decades, significant evidence support their use in iron overload. Both oral drugs are effective in reducing the iron overload and its burden; however, several patient characteristics favor one over another. The understanding of iron toxicity together with its consequences on the organ system is an important aspect of employing therapeutic strategies. Iron-chelation therapy is currently proven to be of advantage against the treatment of several conditions including transfusion-dependent thalassemia and hemoglobinopathies, where the management of iron overload is fundamental strategy to reduce both mortality and morbidity.

On the contrary, the adverse drug effects and high costs associated with chelation therapy has its own consequences leading to prevention of optimal dosing and poor adherence to treatment that may result in an inadequate response in the patients.

Therefore, even though the chelation therapy is available, there are instances of poor adherence due to adverse effects or its administration regimen. The potential advances in chelation therapy through research on animal and cell models could make the future human research possible, unlike OTC chelation therapy that is unapproved and unregulated. The continuous efforts are being made to use the extensive knowledge of iron metabolism in humans and the relevant animal models, for the ongoing research in the drug target, drug structure and physicochemical properties, drug absorption and distribution pathways. With the promising advances in drug discovery and development, there is a huge potential of discovering new drugs to satisfy the need of treatment of iron overdose both in children and adults, thus improving the quality of life of the patients with iron-overload.

REFERENCES

1. Hershko C. Iron loading and its clinical implications. Am J Hematol. 2007;82:1147-1148.

2. Shander A, et al. Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox Sang. 2009;97:185-197.

3. Dusek P, et al. Iron chelation in the treatment of neurodegenerative diseases. J Trace Elem Med Biol. 2016.

4. Cook LS. Therapeutic phlebotomy: a review of diagnoses and treatment considerations. J Infus Nurs. 2010;33:81-88.

5. Assi TB and Baz E. Current applications of therapeutic phlebotomy. Blood Transfus. 2016;12:75-83.

6. Rombout SE, et al. Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE hemochromatosis patients: results from a randomized crossover trial. Transfusion. 2016;56:261-270.

7. Brückl D, et al. Efficacy and safety of erythrocytapheresis and low-dose erythropoietin for treatment of hemochromatosis. J Clin Apher. 2016.

8. Kosnett MJ. Chelation for heavy metals (arsenic, lead, and mercury): protective or perilous. Clin Pharmacol Ther. 2010;88:412-415.

9. FDA. Unapproved Chelation Products: News and events. 2016.

10. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology. 2010;139:393-408.

11. Sampietro M, et al. Iron overload in porphyria cutanea tarda. Haematologica. 1999;84:248-253.

12. Aygun B, et al. Therapeutic phlebotomy is safe in children with sickle cell anaemia and can be effective treatment for transfusional iron overload. Br J Haematol. 2015;169:262-266.

13. Madiwale T and Liebelt E. Iron: not a benign therapeutic drug. Curr Opin Pediatr. 2006;18: 174-179.

14. Fatemi SJ, et al. Removal of cadmium by combining deferasirox and desferrioxamine chelators in rats. Toxicol Ind Health. 2012;28:35-41.

15. Tubafard S and Fatemi SJ. Chelation of bismuth by combining desferrioxamine and deferiprone in rats. Toxicol Ind Health. 2008;24:235-240.

16. Blanusa M, et al. Chelation of aluminium by combining DFO and L1 in rats. Toxicology. 2000;147:151-156.

17. Apotex. FERRIPROX® (deferiprone) Tablets, for Oral Use. 2013.

18. Fernández S, et al. Acute iron intoxication: change in urine color during chelation therapy with deferoxamine. Intensive Care Med. 2014;40:104.

19. Gumber MR, et al. Successful treatment of severe iron intoxication with gastrointestinal decontamination, deferoxamine, and hemodialysis. Ren Fail. 2013;35:729-731.

20. Magdalan J, et al. Fulminant hepatic failure in woman with iron and non-steroidal anti-inflammatory drug intoxication. Hum Exp Toxicol. 2011;30:1106-1111.

21. Howland MA. Risks of parenteral deferoxamine for acute iron poisoning. J Toxicol Clin Toxicol. 1996;34:491-497.

22. Berkovitch M, et al. The efficacy of oral deferiprone in acute iron poisoning. Am J Emerg Med. 2000;18:36-40.

23. Fassos FF, et al. Efficacy of deferiprone in the treatment of acute iron intoxication in rats. J Toxicol Clin Toxicol. 1996;34:279-287.

24. Barr J, et al. Acute iron intoxication: the efficacy of deferiprone and sodium biocarbonate in the prevention of iron absorption from the digestive tract. Vet Hum Toxicol. 1999;41:308-311.

25. Porter JB. Deferoxamine pharmacokinetics. Semin Hematol. 2001;38:63-68.

26. Kontoghiorghe CN and Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. Drug Des Devel Ther. 2016;10:465-481.

27. Saliba AN, et al. Iron chelation therapy in transfusion-dependent thalassemia patients: current strategies and future directions. J Blood Med. 2015;6:197-209.

28. Cappellini MD, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006;107:3455-3462.

29. Pennell DJ, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. Blood. 2006;107:3738-3744.

30. Maggio A, et al. Deferiprone versus deferoxamine in patients with thalassemia major: a randomized clinical trial. Blood Cells Mol Dis. 2002;28:196-208.

31. Wolfe L, et al. Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. N Engl J Med. 1985;312:1600-1603.

32. Brittenham GM, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med. 1994;331:567-573.

33. Dessì C, et al. Thalassemia major between liver and heart: Where we are now. Blood Cells Mol Dis. 2015;55:82-88.

34. Kalpatthi R, et al. Safety and efficacy of high dose intravenous desferrioxamine for reduction of iron overload in sickle cell disease. Pediatr Blood Cancer. 2010;55:1338-1342.

35. Silliman CC, et al. Iron chelation by deferoxamine in sickle cell patients with severe transfusion-induced hemosiderosis: a randomized, double-blind study of the dose-response relationship. J Lab Clin Med. 1993;122:48-54.

36. Kontoghiorghes GJ, et al. Benefits and risks of deferiprone in iron overload in Thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. Drug Saf. 2003;26:553-584.

37. Boelaert JR, et al. Deferoxamine therapy and mucormycosis in dialysis patients: report of an international registry. Am J Kidney Dis. 1991;18:660-667.

38. Orton RB, et al. Ocular and auditory toxicity of long-term, high-dose subcutaneous deferoxamine therapy. Can J Ophthalmol. 1985;20:153-156.

39. Cases A, et al. Ocular and auditory toxicity in hemodialyzed patients receiving desferrioxamine. Nephron. 1990;56:19-23.

40. Barton JC. Chelation therapy for iron overload. Curr Gastroenterol Rep. 2007;9:74-82.

41. Gattermann N. The treatment of secondary hemochromatosis. Dtsch Arztebl Int. 2009;106:499-504.

42. Cappellini MD and Piga A. Current status in iron chelation in hemoglobinopathies. Curr Mol Med. 2008;8:663-674.

43. Kontoghiorghes GJ, et al. Advances in iron overload therapies. prospects for effective use of deferiprone (L1), deferoxamine, the new experimental chelators ICL670, GT56-252, L1NA11 and their combinations. Curr Med Chem. 2005;12:2663-2681.

44. Kontoghiorghes GJ, et al. Iron chelation therapy in hereditary hemochromatosis and thalassemia intermedia: regulatory and non regulatory mechanisms of increased iron absorption. Hemoglobin. 2010;34:251-264.

45. Matsui D, et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. Clin Pharmacol Ther. 1991;50:294-298.

46. Vermylen C. What is new in iron overload. Eur J Pediatr. 2008;167:377-381.

47. Maggio A, et al. Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials. Blood Cells Mol Dis. 2011;47:166-175.

48. Hoffbrand AV, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood. 1998;91:295-300.

49. Galanello R. Deferiprone in the treatment of transfusion-dependent thalassemia: a review and perspective. Ther Clin Risk Manag. 2007;3:795-805.

50. Jamuar SS and Lai AH. Safety and efficacy of iron chelation therapy with deferiprone in patients with transfusion-dependent thalassemia. Ther Adv Hematol. 2012;3:299-307.

51. Al Refaie FN, et al. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral Iron Chelators. Br J Haematol. 1995;91: 224-229.

52. www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm275836

53. Kwiatkowski JL. Current recommendations for chelation for transfusion-dependent thalassemia. Ann N Y Acad Sci. 2016;1368:107-114.

54.   Piga A, et al. Deferiprone. Ann N Y Acad Sci. 2010;1202:75-78.

55.   Eckes EJ. Chelation therapy for iron overload: nursing practice implications. J Infus Nurs. 2011;34:374-380.

56.   Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011;364:146-156.

57.   Olivieri NF, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med. 1998;339:417-423.

58.   Bartlett AN, et al. Long-term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). II. Clinical observations. Br J Haematol. 1990;76:301-304.

59.   Castriota SA and Sacco M. Agranulocytosis, arthritis and systemic vasculitis in a patient receiving the oral iron chelator L1 (deferiprone). Br J Haematol. 1997;96:254-255.

60.   Novartis. JADENU/EXJADE® (deferasirox) Tablets, for Oral Use. 2015.

61.   Nick H, et al. Development of tridentate iron chelators: from desferrithiocin to ICL670. Curr Med Chem. 2003;10:1065-1076.

62.   Nisbet BE, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2003;361:1597-1602.

63.   Séchaud R, et al. Absolute oral bioavailability and disposition of deferasirox in healthy human subjects. J Clin Pharmacol. 2008;48:919-925.

64.   Weiss HM, et al. In vitro blood distribution and plasma protein binding of the iron chelator deferasirox (ICL670) and its iron complex Fe-[ICL670]2 for rat, marmoset, rabbit, mouse, dog, and human. Drug Metab Dispos. 2006;34:971-975.

65.   Tanaka C. Clinical pharmacology of deferasirox. Clin Pharmacokinet. 2014;53:679-694.

66.   Cassinerio E, et al. A 5-year follow-up in deferasirox treatment: improvement of cardiac and hepatic iron overload and amelioration in cardiac function in thalassemia major patients. Ann Hematol. 2015;94:939-945.

67.   Pennell DJ, et al. A 1-year randomized controlled trial of deferasirox vs. deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). Blood. 2014;123:1447-1454.

68.   Taher A, et al. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia: the ESCALATOR study. Eur J Haematol. 2009;82:458-465.

69.   Glickstein H, et al. Action of chelators in iron-loaded cardiac cells: Accessibility to intracellular labile iron and functional consequences. Blood. 2006;108:3195-3203.

70.   Wood JC, et al. Deferasirox and deferiprone remove cardiac iron in the iron-overloaded gerbil. Transl Res. 2006;148:272-280.

71.   Vlachaki E, et al. Five Years of Deferasirox Therapy for Cardiac Iron in β-Thalassemia Major. Hemoglobin. 2015;39:299-304.

72.   Pennell DJ, et al. Efficacy of deferasirox in reducing and preventing cardiac iron overload in beta-thalassemia. Blood. 2010;115:2364-2371.

73.   Pennell DJ, et al. Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with β-thalassemia major. Haematologica. 2012;97:842-848.

74.   Ricchi P and Marsella M. Profile of deferasirox for the treatment of patients with non-transfusion-dependent thalassemia syndromes. Drug Des Devel Ther. 2015;9:6475-6482.

75.   Wood JC, et al. The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. Blood. 2010;116:537-543.

76.   Piga A, et al. Deferasirox for cardiac siderosis in β-thalassaemia major: a multicentre, open label, prospective study. Br   J Haematol. 2014;167:423-426.

77.   Pathare A, et al. Deferasirox (Exjade) significantly improves cardiac T2* in heavily iron-overloaded patients with beta-thalassemia major. Ann Hematol. 2010;89:405-409.

78.   Wood JC, et al. Follow-up report on the 2-year cardiac data from a deferasirox monotherapy trial. Am J Hematol. 2012;85:818-819.

79.   Piga A, et al. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. Haematologica. 2006;91:873-880.

80.   Vichinsky E, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron

overload in sickle cell disease. Br J Haematol. 2007;136:501-508.

81. Galanello R, et al. Phase II clinical evaluation of deferasirox, a once-daily oral chelating agent, in pediatric patients with beta-thalassemia major. Haematologica. 2006;91:1343-1351.

82. Hider RC, et al. Deferitazole, a new orally active iron chelator. Dalton Trans. 2015;44:5197-5204.

83. Kwiatkowski JL. Management of transfusional iron overload - differential properties and efficacy of iron chelating agents. J Blood Med. 2011;2:135-149.

84. https://clinicaltrials.gov/ct2/results?term=deferitazole

85. Nurchi VM, et al. Chemical features of in use and in progress chelators for iron overload. J Trace Elem Med Biol. 2016.

86. Borgna PC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004;89:1187-1193.

87. Oudit GY, et al. Role of L-type Ca^{2+} channels in iron transport and iron-overload cardiomyopathy. J Mol Med. 2006;84:349-364.

88. Oudit GY, et al. L-type Ca^{2+} channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. Nat Med. 2003;9:1187-1194.

89. Fernandes JL, et al. A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major. Blood. 2016.

90. Fernandes JL, et al. Amlodipine reduces cardiac iron overload in patients with thalassemia major: a pilot trial. Am J Med. 2013;126:834-837.

91. Ludwiczek S, et al. Ca^{2+} channel blockers reverse iron overload by a new mechanism via divalent metal transporter-1. Nat Med. 2007;13:448-454.