Trends in Peptide and Protein Sciences
Volume 9 (2024): e5

DOI: https://doi.org/10.22037/tpps.v9i1. 46862

Mini-Review Article

Iron Regulatory Proteins and Pharmacological Iron Modulators: Therapeutic Implications

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Article history:
Received: 20 October 2024
Accepted: 26 December 2024

Keywords:
Deferoxamine
Deferasirox
Hemostasis
Iron

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HIGHLIGHTS

- Iron regulatory proteins are essential for maintaining iron homeostasis in the body.
- Iron overload, or hemochromatosis, occurs when the body accumulates excess iron.
- Iron overload leads to toxicity and potential damage to various organs.
- Deferoxamine is an injectable iron chelator that binds excess iron, facilitating its excretion.
- Deferasirox is an oral iron chelator for patients requiring long-term treatment of iron overload.

ABSTRACT

Iron homeostasis in the human body is precisely regulated, primarily through the action of proteins such as hepcidin, produced by the liver. Hepcidin plays a crucial role in controlling iron release by binding to ferroportin, the exporter of iron from cells into circulation. Under normal conditions, absorbed iron effectively binds to transferrin for transport to various tissues. However, individuals with blood disorders requiring frequent blood transfusions are susceptible to iron overload. This condition arises because the body's mechanisms for iron excretion become overwhelmed, leading to chronic accumulation of excess iron. Additionally, dysregulation of iron-related proteins, such as ferritin and transferrin receptors, can further complicate this imbalance in iron homeostasis. This review focused on iron hemostasis and the pharmacological treatments available for managing iron overload, with a particular focus on Deferoxamine and Deferasirox. These medications aim to chelate excess iron, promoting its excretion and alleviating the detrimental effects associated with chronic iron accumulation. By understanding the pathways and proteins involved in iron regulation, as well as the available treatment options, better strategies can be developed to address the challenges faced by patients with iron overload due to frequent blood transfusions.

Cite this article as: Pirivand, F. and K. Ramezani, (2024). Iron regulatory proteins and pharmacological iron modulators: implications for health and disease. *Trends Pept. Protein Sci.,* **9**: e5.

Introduction

Iron homeostasis is a complex process involving various proteins and regulatory mechanisms. Recent discoveries have illuminated the intricate relationships among these proteins and their potential as therapeutic targets for disorders related to iron (Crielaard et al., 2017).

Enterocytes play a crucial role in the uptake and transport of iron (Duck and Connor, 2016). Key proteins, such as iron regulatory proteins, the hereditary hemochromatosis protein (HFE)–transferrin receptor complex, and hephaestin, regulate iron transport across the intestinal epithelium (Roy and Enns, 2000). The hepcidin-ferroportin axis is recognized as a significant modulator of intestinal HIF-2 (hypoxia-inducible factor-2), which regulates iron absorption and the relationship between oxygen metabolism and the regulation of iron levels in the body (Renassia and Peyssonnaux, 2019). Furthermore, research has clarified how erythroferrone suppresses liver hepcidin, thereby increasing iron availability (Kautz et al., 2015).

Moreover, studies have shown that immune cells, including macrophages, T cells, and B cells, require adequate iron for their proliferation and effective functioning. Iron acts as a co-factor in several processes, such as TLR4 signaling, mitochondrial respiration, and epigenetic modifications (Mu et al., 2021). This highlights the complex interplay between iron homeostasis and the immune system, with implications for both inflammatory diseases and infectious conditions (Nairz and Weiss, 2020).

In fact, the growing understanding of proteins involved in iron homeostasis has led to the development of novel therapeutic approaches. Drugs targeting hepcidin, including agonists, stimulators, and antagonists, show promise as treatments for iron disorders (Rana and Prabhakar, 2021). Additionally, drugs that stabilize or inhibit HIF are emerging as potential treatments for diseases associated with iron dysregulation (Renassia and Peyssonnaux, 2019). These advancements in our understanding of iron metabolism have significantly improved our ability to diagnose and manage iron-related disorders, offering new therapeutic roadmaps for related human diseases such as various cancers (Guo et al., 2021).

Iron hemostasis and related disease

The human body, with a complex homeostasis mechanism, balances the absorption of iron from the intestine and the release of stored iron with its own needs. Various molecules such as hepcidin (Ganz and Nemeth, 2012), ferritin (Kunireddy et al., 2018), and ferroportin (Drakesmith et al., 2015) or iron-regulated transporter 1 (Galy et al., 2024) are responsible for the precise regulation of this process and help iron homeostasis (Fig. 1).

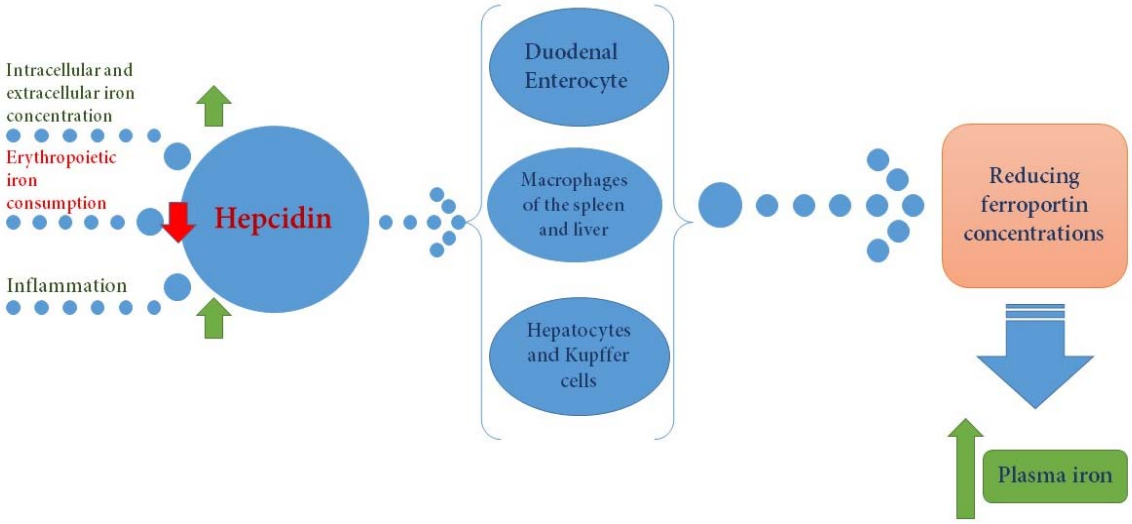

Figure 1. Hepcidin has a central role in the maintenance of iron homeostasis. Hepcidin is essential for iron hemostasis. Its production is influenced by a variety of factors; such as intra- and extra-cellular iron levels. As well, during times of inflammation, the body signals to increase hepcidin. Conversely, during the high production of red blood cells (which happens when we are low on iron), hepcidin production goes down. This hormone helps manage the amount of iron by regulating ferroportin, a protein that allows iron to be exported from specific cells like those in the intestines, as well as macrophages in the spleen and liver, and liver cells themselves. Data was retrieved from (Agarwal and Yee, 2019).

Under typical circumstances, nearly all iron is absorbed and quickly attached to transferrin, which is a plentiful protein that binds iron with high affinity. About 30% of the binding sites on transferrin are occupied by iron (Eid et al., 2014). In patients who undergo large-volume blood transfusions, iron that is not associated with transferrin starts to build up. This plasma iron, a form of non-transferrin-bound iron that can be chelated, is easily taken up by cells, leading to an increase in the cellular iron pool and the production of reactive oxygen species. This ultimately causes cellular dysfunction and death (Fig. 2). For patients requiring frequent blood transfusions, this accumulation of iron can result in chronic iron overload (Pinto and Forni, 2020).

Because of the lack of a controlled mechanism for the elimination of extra iron, patients with frequent blood transfusions suffer from intolerable chronic iron overload (Shander et al., 2009). Despite the changes in the absorption of iron by food and its elimination in bleedings, the concentration of iron in the plasma remains in the range of 10 to 30 μM. It has been shown that liver hepcidin acts as a systemic iron-regulating hormone in experiments conducted on laboratory rodents (Steere et al., 2012). Each unit of red blood cells injected brings 200 to 250 mg of iron into the body, and iron overload occurs after about ten to twenty blood transfusions (Linder and Chou, 2021). Transfused iron overload occurs in patients with a wide variety of blood disorders, including thalassemia (Taher and Saliba, 2017), sickle cell disease (Coates and Wood, 2017), myelofibrosis (Carreau et al., 2016), myelodysplastic syndromes (MDS) (Gattermann, 2018), and aplastic anemia (Pan et al., 2023). It should be considered that inefficient erythropoiesis (beta-thalassemia major) seen in patients with non-transfusion-dependent thalassemia syndrome (NTDT) (Sleiman et al., 2018), can lead to clinical iron overload due to amplified iron absorption from the gastrointestinal tract (Chalmers and Shammo, 2016).

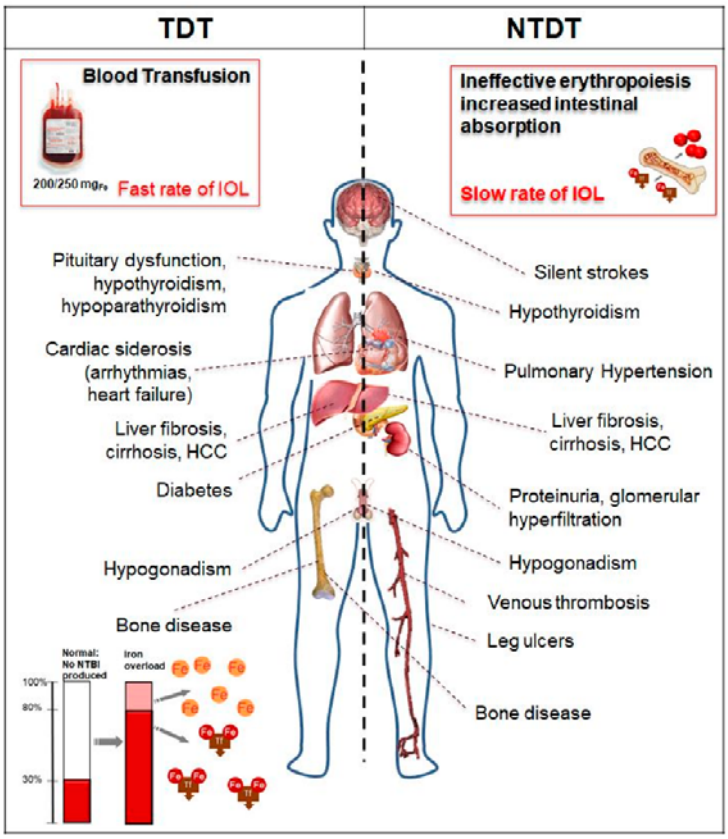

Figure 2. Symptoms and Complications of chronic iron overload (Pinto and Forni 2020). Iron overload (IOL), Transfusion-dependent thalassemia (TDT), Non-transfusion-dependent thalassemia (NTDT), Hepatocellular carcinoma (HCC), Non-transferrin-bound iron (NTBI), Iron (Fe), Transferrin (Tf). The article was published under an open access Creative Common CC BY license.

In individuals with non-injection-dependent thalassemia (Sleiman et al., 2018), ineffective erythropoiesis leads to lower levels of hepcidin, which results in increased iron absorption from the intestines. This condition can subsequently cause iron overload. Iron is continuously retained and repurposed in both heme and non-heme enzymes (Gardenghi et al., 2007; Rivella, 2012).

Iron poisoning usually damages the liver, heart, and endocrine system and can lead to death. For example, in thalassemia without the use of iron chelators, death from heart failure or arrhythmia usually occurs at a very young age. The average age of death in thalassemia patients before the prevalent use of chelating agents, was around seventeen years old, research has shown that the survival rate of patients improved after the introduction of chelating agents (Farmakis et al., 2020). A review of several decades of recorded data for β-thalassemia patients in England shows that survival at the age of 24 years can be attributed to the use of chelating agents (Modell et al., 2000).

Iron is an essential metal element of the brain (DeBenedictis et al., 2020), but excess iron increases oxidative stress (Puntarulo 2005) and causes tissue damage (Lele et al., 2009; Chakurkar et al., 2021) by breaking down hydroxyl radicals to accelerate lipid peroxidation. As a result, it raises the likelihood of developing heart failure, liver cirrhosis, and cancer, as well as conditions like arthritis, dyslipidemia, diabetes, and issues with gonadal function. Additionally, it may be linked to various neurodegenerative disorders, including Alzheimer's and Parkinson's diseases (Villalón-García et al., 2023).

Hereditary hemochromatosis (primary iron overload) is a genetic disorder characterized by increased iron absorption in the intestines and iron deposition in parenchymal tissues which leads to premature death (Joshi et al., 2021). In addition, patients with hemoglobinopathies such as thalassemia major, sickle cell anemia, aplastic anemia, myelodysplastic syndrome, or Diamond-Blackfan anemia require frequent blood transfusions, which can cause secondary iron overload due to the absence of an effective physiological path to eliminate iron (Kang et al., 2019).

Internal regulation of iron homeostasis

Iron regulatory proteins (IRPs)

IRPs (IRP1 and IRP2) are key cytoplasmic proteins that post-transcriptionally regulate iron metabolism by binding to iron-responsive elements (IREs) in target mRNAs. This binding affects the translation of proteins involved in iron uptake, storage, and release (Cairo and Recalcati, 2007). Under low iron conditions, IRPs stabilize mRNAs for transferrin receptor 1 (TfR1) and divalent metal transporter 1 (DMT1), enhancing iron uptake. Conversely, in high iron conditions, IRPs decrease the translation of ferritin and ferroportin (FPN), promoting iron storage and limiting absorption (Vogt et al., 2021).

Hepcidin peptide hormone

Hepcidin is a peptide hormone produced by the liver that regulates systemic iron levels. It acts primarily by binding to ferroportin on cell membranes, leading to its degradation and reducing iron export from enterocytes and macrophages into the bloodstream (Kowdley et al., 2021). Hepcidin expression is influenced by serum iron levels, erythropoietic demand, inflammation, and hypoxia. Increased hepcidin levels lead to decreased intestinal iron absorption, while low levels promote absorption (Clara et al., 2020).

Signaling pathways

Hypoxia-inducible factor-2α (HIF2α) is a transcription factor that regulates erythropoietin synthesis in response to oxygen levels and is also involved in the regulation of iron homeostasis through its interaction with IRPs (Shah and Xie, 2014). In addition, inflammatory cytokines such as IL-6 could elevate hepcidin levels, resulting in impaired iron availability for erythropoiesis, and contributing to anemia of inflammation (Marques et al., 2022).

External regulation of iron levels by drugs

Deferoxamine

Deferoxamine is an iron-chelating agent used clinically to treat conditions of chronic iron overload, such as thalassemia or multiple blood transfusions. It binds free ferric ions in the bloodstream, promoting their excretion via urine. By reducing serum iron levels, deferoxamine indirectly influences hepcidin production. Lower hepcidin levels can enhance intestinal absorption of dietary iron when needed (Jones et al., 2020).

Deferoxamine (DFO) drug known as Desferal is the first medicine used to treat iron overload. This drug is a siderophore produced by the bacterium Streptomyces

pilosus and was discovered by Keberle and her colleagues in 1964 (Keberle, 1964), and was approved for medical use by the US Food and Drug Administration (FDA) in 1968 Deferoxamine is a hexadentate iron chelator with a chemical structure of C25H48N6O8 and a molecular weight of 560.68 g/mol (Flora and Pachauri, 2010). The half-life of pure DFO is very short and ranges from 5 to 15 minutes (Xu et al., 2020).

Deferoxamine is a chelator drug that has a tendency to absorb iron much more than other metals such as zinc, calcium, or magnesium. The volume of distribution of this molecule is from 0.6 to 1.33 liters per kilogram. Deferoxamine is extensively metabolized in plasma and turns into several metabolites (A to F), and metabolite B may be toxic. Deferoxamine is converted to ferrioxamine by absorbing iron cations, this connection changes deferoxamine from a molecule with a direct chain structure to a stable octahedral compound with completely different pharmacokinetic properties. The volume of distribution of ferrioxamine is much less than deferoxamine (about 0.2 liters/kg), which shows that this molecule remains exclusively in the extracellular fluid (Umemura et al., 2017). About 100 mg of deferoxamine is capable of binding approximately 8.5 mg of trivalent iron (Prisciandaro et al., 2013). If iron chelation occurs in hepatocytes, it is excreted by bile, and if it occurs in blood plasma or other tissues, it is excreted by kidneys. Deferoxamine is capable of removing iron from transferrin and ferritin, but it cannot remove iron from hemoglobin. Deferoxamine can also bind to aluminum in plasma and turn into aluminoxamine, which is excreted through the kidneys. DFO can pull aluminum deposited in the tissue into the plasma. DFO can pull aluminum deposited in the tissue into the plasma. For this reason, patients with measured serum aluminum concentrations greater than 200 µg/L should not be treated with DFO as it may lead to extremely high aluminum levels and fatal neurotoxicity (Mobarra et al., 2016).

Oral chelator, deferasirox

Similar to deferoxamine, other chelators may also be employed to manage iron overload conditions. These drugs can help restore balance in patients with dysregulated iron metabolism. Deferasirox is the most popular one. Deferasirox (Exjade) is the first active oral iron-chelating drug that is popular for routine use in the United States. This drug is used to treat chronic iron overload caused by repeated blood transfusions in patients older than two years (Cappellini and Taher, 2009; Shah, 2017). Deferasirox with molecular formula $C_{21}H_{15}N_3O_4$ and chemical name: (4-[3,5-bis-(2-hydroxyphenyl)-[1,2,4]-triazol-1-yl] benzoic acid) is prepared from salicylic acid during a two-step process (Stumpf, 2007). This drug has a molecular mass of 373.4 g/mol and a pH of 4.1 in water at a temperature of 22 to 24 degrees Celsius. Deferasirox is made in the form of tablets so that it can be easily used by children and adults, and it dissolves in water and juice (Tanaka, 2014). Deferasirox has a relatively long half-life in plasma, i.e. 11 to 19 hours (Porter, 2010).

Deferasirox is a new class of oral chelators called B hydroxyphenyl triazole. This triple molecule has three active sites for binding to iron and binds to iron with a ratio of 2:1 (Porter, 2010). Triple chelators need two ligand molecules to bind to one iron atom. This drug is first secreted into the biliary system and 84% is eliminated through feces. At least 8% of it is subjected to oxidative metabolism by cytochrome P450 and only 8% is excreted by the kidney (Stumpf, 2007).

Deferasirox reduces iron overload by increasing the hepcidin hormone (Manduzio, 2015). Hepcidin regulates iron absorption by reducing the expression of ferroportin (membrane protein responsible for the transfer of intracellular iron to the bloodstream, which is on the surface of the intestinal basement membrane) (Zhang et al., 2011).

Therapeutic implications

The interplay between external chelation therapy and internal regulatory mechanisms highlights the potential for targeted treatments that manipulate these pathways. For example, understanding how deferoxamine affects hepcidin could lead to optimized treatment strategies for patients with both iron deficiency and overload (Kontoghiorghes, 2024).

Patients with potentially fatal anemia can be treated with continuous blood transfusions and iron chelate therapy (Brittenham Gary, 2011). The benefits of treatment are not immediately realized because the effectiveness of treatment progresses slowly. Therefore, improving compliance is very important in terms of quality of life and health economics (Strauss and Auerbach, 2018). It seems that drug treatment for iron overload has not yet reached the final stage of evolution and changes are needed (Prabhune et al., 2024).

Applications of deferoxamine

Early use of Deferoxamine according to iron overload reduces the body's iron load and helps to protect against diabetes, heart diseases, and premature death in patients with thalassemia major (Entezari et al., 2022). Previous studies have shown the strong anti-fibrotic effects of deferoxamine, reduction of oxidative stress and subsequent inflammatory cascade, as well as the production of profibrogenic factors. Adding deferoxamine to interferon for the treatment of patients with HCV can be a promising adjuvant method to increase the response to treatment (Darwish et al., 2015). The results of in vitro and in vivo studies show that deferoxamine improves osteoporosis by increasing angiogenesis and bone formation (Jia et al., 2016). Airway tissue ischemia and hypoxia in human lung transplantation is a consequence of the lack of bronchial circulation during the surgical procedure and is a major risk factor for the development of airway anastomotic complications. Excess expression of hypoxia-inducible factor (HIF-1α) causes vascular repair and relieves ischemia and hypoxia of the allograft. A nanoparticle formulation of deferoxamine has been prepared that can be applied locally in airway grafts during surgery (Jiang et al., 2014). Recent studies in the field of deferoxamine indicate various features that can expand the use of this drug in the fields of tissue engineering and regeneration. Due to its ability to overregulate hypoxia-inducible factor (HIF-1α) and other main angiogenic factors, it plays a role as an angiogenic agent in studies related to ischemia, wound healing, and bone regeneration. DFO has also shown antioxidant abilities unrelated to iron chelating properties, making it suitable as a potential modulator of oxidative stress involved in the inflammatory response. Together, these properties make DFO a potential bioactive molecule to promote wound healing (Holden and Nair, 2019).

Deferoxamine increases neovascularization and accelerates diabetic wound healing through the accumulation of HIF-1α and the regulation of endothelial cell function (Hou et al., 2013). Deferoxamine effectively reduces neuronal cell death and improves cognitive function after subarachnoid hemorrhage (Qin et al., 2019). Rapidly growing cancer cells are highly dependent on iron for their survival, so iron-scavenging drugs have potential applications in cancer treatment (Lang et al., 2019). Deferoxamine improves hematopoiesis in patients with anemia such as rheumatoid arthritis, hemolysis, or myelodysplastic syndromes and reduces the dependence on blood transfusion. This effect is related to improving the response of erythropoietin to related anemia (Norbert et al., 2012). The production of free radicals catalyzed by iron causes the oxidation of synovial membranes, which has been proposed as the first event in the inflammation of rheumatoid arthritis. Treatment with DFO to chelate free iron in the joint may reduce this inflammation and prevent the progression of joint damage (Norbert et al., 2012). For the treatment of patients with severe myocardial siderosis and left ventricular dysfunction, the combined treatment of subcutaneous deferoxamine and oral deferiprone is used, which causes a decrease in myocardial iron and improves heart function (Tanner et al., 2008). Aluminum frequently accumulates in patients with severe renal failure, findings show that deferoxamine is useful for the treatment of aluminum accumulation in the bones of patients with renal failure (Charhon, 1990).

Despite the clear advantages of using DFO, a large number of systemic toxicities associated with it have been reported. Hypotension is the most important short-term complication of deferoxamine because it may complicate acute iron poisoning. Allergy and anaphylaxis to deferoxamine are rare. Local erythema and sensitivity can appear after subcutaneous injection of deferoxamine, but if this drug is injected deep into the subcutaneous tissue with a concentration of less than 250 mg/ml of water, this reaction can be minimized. Some abdominal discomforts have been observed after oral administration. Other short-term side effects include: fever, diarrhea, heartburn, leg cramps, skin rash, and itching (Gray and Ray, 2023). As a result of long-term use of chelators, serious side effects may occur. The most common ones are growth failure, bone abnormalities, and hearing impairment. In patients who started using high-dose chelators in the first years of life, a similar pattern with severe deformation of organs and metaphysis has been described. High-frequency sensorineural hearing loss has been described in a large percentage of patients with iron overload during daily DFO therapy, which was associated with single doses and total monthly doses, and was more common in younger subjects with low ferritin levels. Dose reduction leads to significant improvement in patients with mild impairment, while dose reduction is of little benefit to severely affected individuals. Eye, kidney, and lung toxicity has also been described in patients who receive very high doses of DFO. Nevertheless, it is emphasized

that deferoxamine poisoning can be prevented and controlled, while the main cause of death in these patients is hemochromatosis (Musallam et al., 2024).

Applications of deferasirox

Deferasirox activates Nuclear factor kappa B (NF-κB) inhibitors in myelodysplastic syndrome and plays a role in reducing anti-apoptotic factor transcription, which may affect erythroid dysfunction (Messa et al., 2010). This drug suppresses signaling through mTor (a protein kinase that regulates cell growth, survival, metabolism, and immunity) in myeloid leukemia cells (Ohyashiki et al., 2009). Deferasirox is also effective in the management of cardiac siderosis (Piga et al., 2014). In a retrospective study, Deferasirox had a significant improvement in the assessment of bone mineral density in comparison with Deferiprone, Deferoxamine, and the combined use of Deferiprone and Deferoxamine. In addition, it has led to the greatest improvement in endocrine disease (Moukalled et al., 2018). Aceruloplasminemia can show incomplete clinical penetration, but it is directly related to the accumulation of iron in the liver and brain. The accumulation of iron in aceruloplasminemia is the result of a defect in the delivery of iron to the outside of the cell, that is, hepcidin, which is effective in the regulation of cell iron (Finkenstedt et al., 2010). Deferasirox treatment can improve some neurological symptoms, especially cerebellar ataxia, in patients with aceruloplasminemia (Miyake et al., 2020). Deferasirox is effective in reducing serum ferritin and liver iron concentration in patients with iron overload in myelodysplastic syndrome and aplastic anemia, in addition, with deferasirox, one can have positive expectations on blood and liver function (Cheong et al., 2014). Deferasirox is one of the drugs and has shown significant antitumor effects in several in vitro and in vivo studies (Bedford et al., 2013). Deferasirox, by reducing cyclin D1 and inhibiting its related signals, may be a promising adjuvant therapeutic molecule in the treatment strategy of Mantle cell lymphoma (Samara et al., 2021).

Conclusion

Due to the advances in medical science, many chronic diseases that used to lead to early death can now be effectively managed and treated with drug therapy. For example, patients with potentially fatal anemia can be treated with continuous blood transfusions and iron chelate therapy (Kontoghiorghes and Kontoghiorghe, 2020). The benefits of treatment are not immediately realized because the effectiveness of treatment progresses slowly. Therefore, improving compliance is very important in terms of quality of life and health economics (Strauss and Auerbach, 2018). Although chelation therapy is generally poor, the availability of oral iron chelators can help improve patient compliance (Chong et al., 2021). It seems that drug treatment of iron overload has not yet reached the final stage of evolution and new approaches are needed to be able to safely treat the patients (Wang et al., 2021; Kowdley et al., 2023).

Ethical Statement

This work did not contain any animal or human studies performed by the authors.

Competing Interests

The authors have no conflicts of interest to declare.

Funding

This work did not receive any financial support.

Data Availability

All relevant data has been reported in the manuscript.

Authors Contribution

F. Pirivand and K. Ramezani contributed to the manuscript drafting. The final manuscript was reviewed and confirmed by both authors.

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