



Review

Challenges of Iron Chelation in Thalassemic Children

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Abstract: Thalassemia treatment still relies on supportive care, mainly including blood transfusion and iron chelation therapy. Iron chelation is considered the main factor responsible for the marked improvement in survival rates of thalassemic patients. Hemosiderosis may be prevented if appropriate chelation therapy is offered from early childhood, with timely dose adjustments according to changing body weight and close monitoring of organ iron load. With three iron chelators currently available, the choice of appropriate chelation, either as monotherapy or combined therapy, should be individualized depending on the iron overload of target organs, patient's age, presence of adverse events and compliance issues, given known limitations related to each agent's administration.

Keywords: thalassemia; deferoxamine; deferiprone; deferasirox

1. Introduction

Thalassemia is the most common inherited disorder worldwide, characterized by impaired hemoglobin production [1]. The disease is endemic in certain regions, such as the Mediterranean, Sub-saharan Africa, Middle East and Southeast Asia. Due to rising immigration, however, thalassemia can be found in Northern Europe, Australia and Northern America as well [2]. The clinical phenotype varies, depending on the number of affected gene clusters and the underlying mutation, while approximately 60,000 newborns are severely affected every year.

At a molecular level, the genes responsible for hemoglobin synthesis are located in chromosomes 16 and 11, encoding the α - and β -globin chains, respectively. Imbalance in α -/ β -globin synthesis results in ineffective erythropoiesis, chronic hemolytic anemia, compensatory hematopoietic expansion, hypercoagulability and increased intestinal iron absorption [1,3,4]. The first clinical description of thalassemia came 90 years ago from two physicians, namely Cooley and Lee. Ever since that first description, the disease pathophysiology has been extensively studied [3]. Despite all learned information regarding the cellular and molecular basis of thalassemia, particularly during the last 50 years, treatment still relies, almost solely, on supportive care. Conventional management includes blood transfusion and iron chelation therapy, as well as splenectomy, in specific cases. Different therapeutic approaches are currently evolving, targeting the reduction in ineffective erythropoiesis and iron dysregulation, while gene therapy focused on β - or γ -globin modifications has made remarkable progress. The only curative treatment, however, remains allogeneic hematopoietic stem cell transplantation [5].

Regular transfusions in thalassemic pediatric patients aim at ameliorating anemia by suppressing ineffective erythropoiesis, at preventing splenomegaly and skeletal anomalies, and allowing for normal development and growth [6,7]. The frequency of transfusion requirements indicates the severity of the disease [3]. In most cases, patients with transfusion-dependent thalassemia are able to achieve hemoglobin levels between 9 and 10.5 g/L with 10–20 mL/kg of packed red cell transfusions every 2–4 weeks [4,6,8]. According to the Thalassemia International Federation, approximately 200,000 patients receive



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regular transfusions throughout the world, although the actual number of patients might be underestimated, with many not having access to therapy [1].

Although life-saving, transfusion therapy contributes to secondary morbidity. As the transfused erythrocytes are destroyed by macrophages of the reticuloendothelial system, the heme iron that is released binds to transferrin and is used in bone marrow for erythropoiesis. Transferrin saturation exceeds normal levels after the first 4–6 transfusions and, subsequently, iron enters as a non-transferrin-bound form in organs, such as the heart, liver, anterior pituitary gland and pancreas, resulting in cell damage [9,10]. The iron overload arising from transfusions, in addition to excess gastrointestinal absorption, complicates the clinical phenotype, leading to organ dysfunction if left untreated [7,11,12]. By the age of 10 years, transfusion-dependent thalassemic children may already present with cardiomyopathy, liver fibrosis and endocrine dysfunction due to iron accumulation [1]. Mortality of thalassemic patients in the second and third decade of life is largely attributed to iron-related complications in 40% of all cases [3]. Iron chelation therapy aims at maintaining iron levels at safe levels [12]. Magnetic resonance imaging allows for the direct evaluation of iron stores in the heart and liver; however, the technique has not been yet standardized for other organs that accumulate iron as well [13]. Optimization of non-invasive iron assessments and iron chelation treatment are, so far, the tools for the effective management of thalassemia [4].

2. Iron Chelation Therapy

In the absence of a passive excretory mechanism of iron, the removal of excess iron in transfusion-dependent thalassemic patients requires the administration of iron chelation therapy [13]. The iron-chelating agents form a complex with circulating iron, inducing its clearance [14]. Chelation therapy is considered the main responsible factor for the marked improvement in the survival of thalassemic patients [6].

Thalassemic pediatric patients presented with higher transfusion requirements compared to adults, especially at pre-adolescent and adolescent ages, thus achieving normal development and growth, albeit with a greater iron burden. Hemosiderosis may be prevented with appropriate chelation therapy from early childhood, timely dose adjustment according to changing body weight, as well as close monitoring of organ iron overload. Thus, a complication-free survival and a close-to-normal life expectancy may be achieved [15]. Iron overload, though, is a chronic condition for transfusion-dependent thalassemic patients and the benefits of chelation therapy are not immediately perceptible.

Chelation therapy is initiated after the first 10–20 transfusions in children, traditionally around the second year of life, when ferritin levels exceed 1000 ng/mL [9]. Three iron chelators are currently available: deferioxamine, which is parenterally administered, and deferiprone and deferasirox, which are the oral drug alternatives [12] (Table 1). The choice of appropriate chelator is individualized, depending on iron overload in target organs, patient age and compliance issues, ultimately aiming at a stable iron burden with limited drug toxicity [16].

Table 1. Chelation agents' characteristics. DT: dispersible tablet, FCT: film-coated tablet.

Characteristics	Deferioxamine	Deferiprone	Deferasirox
Route of administration	subcutaneous intravenous	oral (tablet or liquid)	oral (DT or FCT)
Dose	20–40 mg/kg/d in 8–24 h	75–100 mg/kg/d Thrice daily	DT: 20–40 mg/kg/d FCT: 14–28 mg/kg/d Once daily
Chelator: iron ratio	1:1	3:1	2:1
Excretion	Urine Stool	Mainly urine	Stool

Table 1. Cont.

Characteristics	Deferioxamine	Deferiprone	Deferasirox
Common adverse events	Injection site reaction Growth impairment Ophthalmotoxicity Otoxicity	Neutropenia Agranulocytosis Gastrointestinal disorders Arthralgia Transaminasemia	Gastrointestinal disorders Nephrotoxicity Skin rash Transaminasemia Liver and renal failure
Advantages	Long experience	More effective in heart hemosiderosis	More convenient dosage regimen
Limitations	Parenteral administration Suboptimal compliance	Weekly blood count monitoring	High cost

3. Deferoxamine

Deferoxamine (DFO) is the first licensed chelating agent, used as a slow subcutaneous or intravenous infusion since 1968. The prognosis of thalassemic patients has dramatically improved after its administration, and for decades, DFO was the only available chelation therapy [15]. DFO is a hexadentate molecule produced by *Streptomyces pilosus*, which presents a dual mechanism of action. It binds free plasma iron and excess iron within cells, at a 1:1 ratio, with 100 mg of DFO binding 9 mg of iron. Iron released by senescent erythrocytes binds firmly to DFO and is excreted unaltered through kidneys, while unbound DFO enters in hepatic parenchymal cells, interacts with intercellular iron and is excreted through the biliary system. DFO also removes iron directly from myocardium [17–19].

Due to the low oral drug bioavailability and short half-life, DFO cannot be orally received and is usually administered subcutaneously for 8–12 h, 5–7 days a week. DFO is approved for transfusion-dependent thalassemic children >2 years old and remains the first-line treatment until the age of 6 years [20,21]. The initiation dose is recommended at 20–30 mg/kg/d, reaching a maximum permissible therapeutic dose of 40 mg/kg/d when growth is complete [9].

Much experience has been accumulated over the years, with DFO proving to be effective in removing excess iron, mainly from the liver, and to a lesser extent from the heart. Common drug-related adverse events include local injection reactions, gastrointestinal disturbances, serum creatinine increase, acute kidney injury and renal tubular disorders [15,21]. Rare systemic allergic reactions, such as urticaria, pruritus and oedema, even if with a successful desensitization procedure, have been reported, as well as acute renal failure attributed to high DFO doses [21–23]. Furthermore, DFO has been associated with dose-dependent ophthalmo- and ototoxicity. In addition, early initiation (before the 3rd year of age) and intensive chelation therapy (doses above 50 mg/kg/d) have been related to severe bone damage and growth failure, limiting chelation potential in early childhood [12,24]. Already in 1988, Piga et al. reported on growth impairment in more than half of prepubertal patients undergoing intensive subcutaneous DFO chelation therapy, remarkably reversible after dose reduction [25]. Case studies in pediatric populations indicate the possibility of a safe profile without serious side effects or need of drug discontinuation when appropriate dose adjustments and close monitoring are applied [12]. Generally, adverse events are considered more common in the presence of low iron burden. Thalassaemic children should be regularly monitored for renal and liver dysfunction, ocular and audiological disorders, as well as growth and bone health impairment [9].

Since the vast majority of DFO adverse events are manageable under close monitoring, the main limitation of DFO for pediatric patients remains the parenteral administration by prolonged subcutaneous infusion, commonly during the night, leading to suboptimal compliance.

4. Deferiprone

Deferiprone (DPF), an oral chelating agent already known since 1984, was not approved until 2011 due to drug-related adverse events and initial concerns regarding its

efficacy [9,26]. DFP is a bidentate lipophilic molecule that binds to iron and forms a 3:1 (DFP:iron) stable complex. It is rapidly absorbed, reaching peak plasma levels 45–60 min after ingestion [27]. DFP is able to enter iron-overloaded tissue cells, including myocytes. After mobilizing intercellular iron, DFP facilitates its transfer to extracellular apotransferrin [19]. The drug–iron complex is finally excreted in the urine. However, only 4% of a DFP single dose is excreted as the complex in patients with iron overload [28].

Clinical trials indicate that DFP results in a significant reduction in iron stores, while a superiority of daily DFP as compared to subcutaneous DFO has been reported regarding the removal of cardiac iron and improvement in cardiac function [20,29]. DFP is available in tablet and liquid formulations, suitable also for children, and can be administered in a dose of 75–100 mg/kg/d every 8 h [15]. DFP has been licensed as a second-line therapy in patients >6 years old in Europe and USA if other chelating agents are contraindicated or inadequate [30]. In specific countries, such as Turkey, DFP has been used as a first-line therapy [9].

Adverse events, however, are relatively common, leading to discontinuation of the medication in 5–10% of patients [28]. The most common side effects include transaminasemia, gastrointestinal disturbances, arthralgia and neutropenia. Agranulocytosis is a severe uncommon side effect, occurring in 0.7% of pediatric patients—more frequently in females—and patients during the first months of treatment, and resolving after DFP cessation [12,28,29]. Agranulocytosis is considered as an idiosyncratic, unpredictable and not dose-dependent reaction [12]. In clinical trials, mortality due to agranulocytosis was zero in contrast to post-marketing surveillance programs that reported an 11% agranulocytosis fatality rate [31].

On the other hand, neutropenia is more commonly seen in pediatric patients (5.3–7.1%), but does not always evolve into agranulocytosis even if DFP therapy is continued [28]. The mechanism of DFP-induced neutropenia remains unclear. An *in vitro* toxic effect of DFP on myelopoiesis has been reported, while animal studies have shown leucopenia following DFP administration in mice both with and without iron overload, so that the toxicity could not be attributed to iron depletion. Alternative mechanisms studied included the DFP interaction with copper, that might lead to copper deficiency, commonly associated with neutropenia, and an immune-mediated hypothesis without, however, conclusive evidence [32].

Close monitoring with complete blood count is recommended for all patients as well as therapy discontinuation in case of detected neutropenia [29]. A clinical study, evaluating the safety and efficacy of the liquid formulation of DFP in 100 children, checked weekly the patients' absolute neutrophil count (ANC) and intensified the monitoring on a daily basis in case of mild neutropenia, without drug interruption, until neutropenia resolution. DFP was only ceased if two consecutive ANC values were below $1.0 \times 10^9/L$ or immediately if the ANC was below $0.5 \times 10^9/L$. The study reported that, in most cases, neutropenia resolved without intervention. In one patient only, agranulocytosis was reported following three episodes of neutropenia [33]. Whether immediate DFP cessation is the most appropriate strategy in the presence of non-severe neutropenia is still to be determined.

Therefore, the main limitations of DFP administration in children remain the risk for agranulocytosis with the need for close lab monitoring. In addition, age-restricted indications have limited its use in young patients in some countries that could take advantage from its relatively low cost.

5. Deferasirox

Deferasirox (DFX) is the newest oral iron chelator that allows for once-daily dosing due to its long half-life (16–18 h). DFX is a tridentate molecule that binds with affinity and specificity to iron in a 2:1 ratio (DFX: iron) [29]. Besides iron, DFX shows an affinity for copper and zinc, however to a much lesser extent, minimizing the risk for these trace elements' depletion [34]. The active DFX molecule is highly lipophilic and circulates *in vivo*

bound to protein [35]. It is rapidly absorbed from the gastrointestinal tract, reaching a maximum plasma concentration 1.5–4 h post dose. The drug is metabolized in the liver and, to a lesser extent, excreted in the urine [36]. According to the DFX pharmacokinetic profile, chelation activity over a 24 h period is provided after once-daily oral administration, while the long-lasting DFX presence in plasma provides efficient protection against the effects of circulating non-transferrin-bound iron [34]. DFX doses at 10, 20 and 40 mg/kg/d lead to mean iron excretions of 0.119, 0.329 and 0.445 mg Fe/kg body weight per day, respectively. These amounts are considered within the clinically relevant target (0.1–0.5 mg/kg/d) [35].

DFX arose as the result of the efforts to develop an orally administered, longer-acting chelating agent with a comfortable dosing regimen, without the potential fatal side effect of agranulocytosis that is connected with the other oral iron chelator DFP [29]. In the USA, DFX was approved in 2005 for children >2 years old with transfusion-dependent thalassemic syndrome and, since then, has been the most commonly prescribed iron chelator [13]. A year later, DFX was approved in Europe for children >6 years old or >2 years old if DFO is contraindicated or deemed inadequate [15]. To date, numerous clinical trials have compared DFX with other available chelators [37]. Therapy with DFX shows long-term efficacy, reducing ferritin levels and iron burden in a dose-dependent manner, in adult and pediatric patients [9,38]. DFX successfully removes the excess iron from the liver and heart, while presenting a safe profile in high dosing regimens and low ferritin levels [39]. DFX presents similar efficacy with DFO, but is superior in terms of compliance compared to both parenterally administered DFO and thrice-daily oral DFP [38]. The largest study comparing DFX with DFO enrolled almost 300 patients in each arm and failed to prove DFX inferiority, possibly due to the underdosing of DFX [39].

Common adverse events include gastrointestinal disorders, with up to 30% of patients experiencing abdominal pain, diarrhea, nausea or vomiting; as well, skin rashes, transaminasemia and serum creatinine increase in approximately one third of patients [9,13]. Nephrotoxicity may occur early following DFX therapy initiation and is usually non-progressive or even reversible. DFX-related Fanconi syndrome has been described in 0.1–1% of patients, more often in children and adolescents under 16 years of age or in elderly patients (over 65 years). DFX discontinuation seems to lead to syndrome resolution, while re-administration may result in syndrome recurrence, though in a milder form [40]. Liver and renal failure, as well as gastrointestinal bleeding, that were in some cases fatal, have also been reported. Most of the serious adverse events, however, have been reported in elder patients with high-risk myelodysplastic syndrome, underlying liver or kidney disease, or thrombocytopenia. Thus, DFX is contraindicated in patients with hepatic or renal impairment, or a platelet count <50,000/ μ L [29]. As for children, there are two case reports related to gastrointestinal hemorrhage in thalassemic pediatric patients on DFX; one of them, however, involves receiving a dose higher than recommended [41,42]. Unlike other chelators, DFX demonstrates a safe profile in pediatric patients with regard to growth and puberty, and is not complicated by agranulocytosis [9,20]. Monotherapy with DFX is considered to have the lowest discontinuation rate (0.2%) due to adverse events [12].

DFX was first released in the formulation of dispersible tablets (DTs), designed to be consumed on an empty stomach in the form of a suspension after mixing with water or juice. However, the preparation was a lengthy process, and the final oral suspension was not palatable and was often related to reduced gastrointestinal tolerability. In addition, bad taste and large volume of the suspension often led to the full amount not being consumed, especially by young patients. A new film-coated tablet (FCT) DFX formulation was developed to overcome these issues and, due to the use of the same active ingredient, its marketing was quickly approved based on the clinical trials run for the original DFX formulation [29]. FCT lacks excipients (lactose and sodium sulfate) responsible for gastrointestinal effects, and can be taken with or without a light meal, offering a more convenient mode of administration [43]. The new formulation shows higher bioavailability than the original one; so, the DFX dosage should be decreased by 30% when switching from DT to

FCT. Therefore, the recommended DFX dose for DT is 20–40 mg/kg/d and for FCT it is 14–28 mg/kg/d [29].

Sparse data are available regarding the safety and efficacy of the newest DFX formulation in children, especially under 10 years of age. A clinical trial comparing the two DFX formulations given over a 6-month period in 150 patients, both adults and children older than 10 years of age, has reported on the new formulation's safety profile and pharmacokinetic properties, as well as patient-related outcomes [44]. A longer, 2-year clinical trial provided additional data regarding long-term DFX FCT efficacy and safety in children and adults. However, only three pediatric patients were enrolled [45]. An exclusively pediatric study, that enrolled patients 2–18 years old, demonstrated that DFX FCT was safe when given in older children, but led to an increase in liver enzyme values in children younger than 6 years, which failed to respond to dose adjustments [46].

The new formulation of DFX hopes to overcome the palatability issues and gastrointestinal disturbances of the original formulation. Pediatric patients, however, should still be regularly monitored, especially regarding liver and kidney function. Last, but not least, the cost of DFX treatment is higher than other chelation therapies, so its administration can be limited in certain countries.

6. Combined Chelation Therapy

Even in compliant patients, monotherapy with the current available chelators may be ineffective in achieving a negative iron balance, while dose increases often lead to toxicity. As the ideal chelation therapy is still to be found, efforts to control iron overload through the combination of available iron chelators are proposed. Combination therapy leads to the continuous presence of chelators in patients' circulation, reducing the toxic-free labile iron that is mainly responsible for organ damage. The most relevant published data, however, refer to adult patients.

The combination of DFO and DFP is the most studied combination. It is considered to be effective in removing excess iron based on the completely different pharmacokinetics of the chelating agents that, however, act in a synergic way. More specifically, DFP penetrates the tissue cells, accesses and mobilizes chelatable iron that is subsequently delivered to DFO—a chelator with a much higher affinity for iron—promoting its excretion [47]. This combination has proved to decrease liver and cardiac iron overload, improving left ventricular function and reversing iron-related endocrinopathies [16]. The oral chelator is administered daily, while a subcutaneous infusion of DFO ranges from 2 to 7 days a week, depending on the patient's iron burden [48]. As for adverse effects, the reported safety profile does not differ from that already known with each chelator monotherapy [47].

An additive effect of DFX and DFO was initially not expected, as DFX circulates and is bound to proteins. Studies in animal models did not show any remarkable effect of combined therapy with DFO and DFX compared to DFX monotherapy in either liver or heart siderosis [49]. The combination, though, in adult patients has demonstrated iron load reduction without unexpected toxicities [50–53]. The HYPERION study evaluated combined DFO and DFX DT therapy in a mean dose of 36.3 mg/kg/d for 5 days and 30 mg/kg/d, respectively, in 60 patients with severe cardiac hemosiderosis. One third of these difficult-to-treat patients achieved a clinically relevant reduction in cardiac and liver iron overload [54]. Clinical studies have also included pediatric patients, aged over 8 years, with severe myocardial and liver siderosis, reporting a reduction in iron overload without additional safety concerns [52,54].

Given that the compliance to the DFO-based combination therapies is expected to be suboptimal due to the parental administration of DFO, a combination of the two oral chelators has also been studied. In cellular models the combination of DFP and DFX presented the greatest synergism compared to all other combinations, with 60% of mobilized iron being attributable to a synergic interaction [55]. Even though clinical reports on the safety and efficacy of DFX and DFP combinations are less than other alternatives, the combination was well tolerated in both children and adults and led to a reduction in iron

overload [56–59]. A more recent clinical study, however, failed to show comparable effects on cardiac iron between the two oral chelators and the combination of DFO and DFP, indicating the need for further investigation of the subject [60].

7. Conclusions

Effective chelation therapy limits treatment-related complications and improves the overall survival of thalassemic patients. Compliance, however, to a daily prescribed treatment remains still a major issue. The lifelong duration, the absence of short-term benefits, the presence of adverse events and the limitations in administration of the available chelating agents are responsible for the suboptimal compliance. Continuous education on the unbreakable relationship between patient adherence and complication-free survival is imperative, while application of all possible combinations of treatment should be considered when monotherapy fails.

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