Review

Challenges of Iron Chelation in Thalassemic Children

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Challenges of Iron Chelation in Thalassemic Children

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Abstract: Thalassemia treatment still relies on supportive care, including mainly blood transfusion and iron chelation therapy. Iron chelation therapy is considered the main responsible factor for the marked improvement in survival of thalassemic patients. Hemosiderosis should 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. Three iron chelators are currently available and the choice of appropriate chelator or their combination in pediatric population is individualized, depending on iron overload in target organs, patient age, adverse events and compliance issues, due to the limitations in their administration.

Keywords: thalassemia; deferoxamine; deferiprone; deferasirox

Introduction

Thalassemia is the most common inherited disorder worldwide, characterized by impaired hemoglobin production. 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. Imbalance in a/β- globin synthesis results in ineffective erythropoiesis, chronic hemolytic anemia, compensatory hematopoietic expansion, hypercoagulability and increased intestinal iron absorption [1–3]. Despite all learned regarding the cellular and molecular basis of thalassemia 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.

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 [4,5]. The frequency of transfusion requirements indicates the severity of the disease [2]. In most cases, patients with transfusion dependent thalassemia are able to achieve hemoglobin levels between 9-10,5g/L with 10-20ml/kg of packed red cell transfusions every 2-4 weeks [3,4,6]. According to Thalassemia International Federation, approximately 200,000 patients are receiving 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. The iron overload arising from transfusions, in addition to excess gastrointestinal absorption, complicates the clinical phenotype, leading to organ damage if left untreated [5,7,8]. By the age of 10 years, transfusion dependent thalassemic children may already present cardiomyopathy, liver fibrosis and endocrine dysfunction due to iron accumulation [1]. Mortality of thalassemic patients in the 2nd and 3rd decade of life is largely attributed to iron related complication in 40% of all cases [2]. Iron chelation therapy aims at maintaining iron levels at safe levels [8]. Optimization of non-invasive iron assessment and iron chelation treatment are, so far, the tools for effective management of thalassemia [3].

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Iron Chelation therapy

In the absence of passive excretory mechanism of iron, the removal of excess iron in transfusion dependent thalassemic patients requires the administration of iron chelation therapy [9]. The iron chelating agents form a complex with circulating iron, inducing its clearance [10]. Chelation therapy is considered the main responsible factor for the marked improvement in survival of thalassemic patients [4].

Thalassemic pediatric patients present higher transfusion requirements, compared to adults, especially at pre- and adolescent age, so as to achieve 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 [11]. 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 level exceed 1000 ng/ml [12]. Three iron chelators are currently available: deferioxamine, which is parenterally administered, and deferiprone and deferasirox, which are the oral drug alternatives [8]. 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 [13].

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 [11]. Due to the low oral drug bioavailability and the short half-life, DFO cannot be orally received and is usually administered subcutaneously for 8-12 hours, 5-7 days a week [14]. DFO is approved for transfusion dependent thalassemic children >2 years old and remains the first-line treatment until the age of 6 years [14]. 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 [12].

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 and gastrointestinal disturbances, while serum creatinine increase, acute kidney injury and renal tubular disorders have been also reported [11,15]. Furthermore, DFO has been associated with dose dependent ophthalmo- and ototoxocity. in addition, early and intensive chelation therapy with DFO has been related to severe bone damage and growth impairment, limiting chelation potential in early childhood. Case studies in pediatric populations indicate a the possibility of a safe profile, without serious side effects or need of drug discontinuation when appropriate dose adjustments and close monitoring is applied [8]. Generally, adverse events are considered more common in the presence of low iron burden. Thalassemic children should be regularly monitored for renal and liver dysfunction, ocular and audiological disorders, as well as growth and bone health impairment [12].

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 [12] [16]. DFP is rapidly absorbed and the drug-iron complex is excreted in the urine [17].

Clinical trials indicate that DFP results in a significant reduction of iron stores, while a superiority of daily DFP as compared to subcutaneous DFO has been reported regarding the removal of cardiac iron and improvement of cardiac function [14,18]. 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 hours [19]. DFP has been licensed as second line therapy in patients >6 years old in Europe

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and USA, if other chelating agents are contraindicated or inadequate [20]. In specific countries, such as Turkey, DFP has been used as first line therapy [12].

Adverse events, however are relatively common, leading to discontinuation of the medication in 5-10% of the patients [17]. 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 [8,17,18]. Agranulocytosis is considered as an idiosyncratic, unpredictable and not dose-dependent reaction [8]. On the other hand, neutropenia is more commonly seen in pediatric patients (5.3-7.1%), however, without evolving in to agranulocytosis even if DFP therapy is continued [17]. Close monitoring with complete blood count is recommended for all patients [18].

Deferasirox

Deferasirox (DFX) is the newest oral iron chelator, that allows for once-daily dosing due to its long half-life [18]. It is rapidly absorbed, reaching maximum plasma concentration 1.5-4 hours post dose. The drug is metabolized in the liver and, to a lesser extent, excreted in the urine [21]. According to DFX pharmacokinetic profile, chelation activity over a 24-hour 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 [22].

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 [18]. In 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 [9]. A year later DFX was approved in Europe for children >6 years old or >2 years old if DFO is contraindicated or deemed inadequate [11]. To date, numerous clinical trials have compared DFX with other available chelators [23]. Therapy with DFX shows long-term efficacy, reducing ferritin level and iron burden in a dose dependent manner, in adult and pediatric patients [12,24]. DFX successfully removes excess iron from the liver and the heart, while presenting a safe profile in high dosing regimens and low ferritin levels [25]. DFX presents similar efficacy with DFO, but is superior in terms of compliance compared to both parenterally administered DFO and thrice-daily oral DFP [23].

Common adverse events include gastrointestinal disorders, skin rash, transaminasemia and serum creatinine increase in approximately one third of patients [9][12]. Unlike other chelators, DFX demonstrates a safe profile in pediatric patients with regards to growth and puberty, and is not complicated by agranulocytosis [12,14]. Monotherapy with DFX is considered to have the lowest discontinuation rate (0.2%) due to adverse events [8].

DFX was first released in the formulation of dispersible tablets (DT), 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 not palatable and 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, it's marketing was quickly approved based on the clinical trials run for the original DFX formulation [18]. 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 [26].

Sparse data is 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 [27]. 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

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enrolled [28]. 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 of liver enzyme values in children younger than 6 years, which failed to respond to dose adjustments [29].

Combined Chelation Therapy

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

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 [30]. This combination has proved to decrease liver and cardiac iron overload, improving left ventricular function and reversing iron-related endocrinopathies [13]. The oral chelator is administered daily, while subcutaneous infusion of DFO ranges from 2 to 7 days a week, depending on the patient's iron burden [31]. As for adverse effects, reported safety profile does not differ from that already known with each chelator monotherapy [30].

Even though an additive effect of DFX and DFO was initially not expected, as DFX circulates bound to proteins, the combination in adult patients has demonstrated iron load reduction without unexpected toxicities. Clinical studies have also included pediatric patients, aged over 8 years, with severe myocardial and liver siderosis, reporting reduction in iron overload without additional safety concerns [32,33].

Given that the compliance to the DFO-based combination therapies is expected to be suboptimal due to the parental administration of DFO, combination of the two oral chelators has been also studied. Both in adult and children, combination was well tolerated and led to reduction of iron overload [34–37].

Conclusion

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 life long 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.

Conflicts of Interest: The authors declare no conflict of interest.

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