Deferasirox (Exjade®) for the Treatment of Iron Overload

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Key Words

Chelation • Deferasirox • Myelodysplastic syndromes • Pediatric anemia • Sickle cell disease • Thalassemia

Abstract

Deferasirox is a once-daily oral iron chelator with established dose-dependent efficacy in both adult and pediatric patients with transfusional iron overload. The clinical development program has demonstrated the efficacy of deferasirox for up to 4.5 years of treatment in patients with various underlying anemias, including β -thalassemia, myelodysplastic syndromes, sickle cell disease, aplastic anemia, and other rare anemias. In addition to reducing key indicators of total body iron levels (serum ferritin, liver iron concentration, and toxic labile plasma iron), deferasirox has also demonstrated the ability to remove cardiac iron and prevent future cardiac iron accumulation. Emerging long-term data confirm the tolerability profile of deferasirox, and data on patient compliance render deferasirox a suitable therapeutic option for patients with chronic conditions requiring ongoing iron chelation therapy. Data continue to accumulate in a wide range of patient groups, including those with non-transfusion-dependent anemias such as hereditary hemochromatosis.

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Introduction

Long-term red blood cell transfusion for the treatment of various chronic anemias inevitably leads to the accumulation of iron in the body. Several iron chelators have been developed, designed to mobilize tissue iron by forming complexes that are excreted in the feces and/or urine. Deferoxamine (Desferal®; DFO; Novartis Pharma, Basel, Switzerland) was developed more than 40 years ago and the wealth of clinical experience in iron-overloaded patients has established a role for iron chelators in the improvement of patient quality of life and overall survival [1, 2]. However, due to its poor oral bioavailability and short plasma half-life, subcutaneous administration is required 5–7 days/week, often resulting in poor compliance [3]. Deferiprone (Ferriprox®; Apotex, Toronto, Ont., Canada) was the first oral iron chelator available in the European Union and a number of countries outside the USA and Canada for the second-line treatment of iron overload in adult patients with β -thalassemia in whom DFO therapy is contraindicated or inadequate (European Medicines Agency). Deferiprone has a short half-life (3–4 h) and therefore requires three-times daily dosing. Deferasirox (Exjade®; Novartis Pharma) was developed as a once-daily oral iron chelator through a rational drug development program and represents a new class of tridentate iron chelators. Deferasirox is currently approved in

Fig. 1. Impact of transfusional iron intake and deferasirox dose on LIC. (This research was originally published by Cohen et al. [12] in *Blood*.)

many countries worldwide for the treatment of chronic iron overload due to blood transfusions in patients aged ≥ 2 years. The efficacy and safety of deferasirox has been evaluated in patients with β -thalassemia and also in a wide range of patients with other underlying anemias, including myelodysplastic syndromes (MDS), sickle cell disease (SCD), aplastic anemia (AA), Diamond-Blackfan anemia (DBA), and various other rare anemias [3–11].

Thalassemia

The symptoms of β -thalassemia major occur as a result of complete or partial reduction in the production of the β -globin protein (due to mutations in the β -globin gene) that constitutes part of functional hemoglobin. This results in ineffective erythropoiesis and hemolysis causing severe life-threatening anemia, which normally presents in the 1st year of life and can be fatal during infancy or childhood if untreated. Red blood cell transfusions are the primary treatment approach and are often required from early childhood.

Deferasirox Therapy in Patients with β -Thalassemia Major

The pharmacokinetic profile of oral deferasirox was established in patients with β -thalassemia in two small, randomized, double-blind, placebo-controlled, dose-finding studies [3, 4]. The pharmacokinetic profile, in particular the observed half-life for deferasirox (11–19 h), was sup-

portive of a once-daily dosing regimen as deferasirox plasma levels were maintained within the therapeutic range over a 24-hour period providing continuous chelation coverage [4]. Deferasirox 20 mg/kg/day was also identified as an effective oral dose and shown to be generally well tolerated [3]. Furthermore, deferasirox 20–30 mg/kg/day was shown to be as effective in reducing liver iron concentration (LIC) as DFO at a dose of 40 mg/kg/day [10]. Additional analyses of these data demonstrated that ongoing transfusional iron loading affects the response to deferasirox and, together with serum ferritin trends, needs to be monitored on an ongoing basis and used to guide deferasirox dosing in order to achieve individual patient therapeutic goals of either maintenance or reduction in iron load (fig. 1) [8, 12]. This approach was evaluated in the EPIC (Evaluation of Patients' Iron Chelation) trial where the deferasirox dose was titrated every 3 months according to serum ferritin trends and safety markers [7]. Data from a large group ($n = 937$) of regularly transfused patients with β -thalassemia major showed that changes in serum ferritin were reflective of dose adjustments and mean iron intake during treatment. Patients who received an average actual dose ≥ 30 mg/kg/day had the greatest reduction in serum ferritin (-962 ng/ml; $p < 0.0001$ vs. baseline) and patients receiving <20 or ≥ 20 – <30 mg/kg/day maintained their iron balance [13]. In a retrospective analysis including a large number of patients with β -thalassemia, doses >30 mg/kg/day were shown to safely reduce serum ferritin, which is important for heavily transfused patients who may require higher deferasirox doses to reduce body

iron burden [14]. As well as affecting serum ferritin levels and LIC, deferasirox can also reduce levels of labile plasma iron (LPI) in patients with β -thalassemia major. LPI is a directly chelatable form of non-transferrin-bound iron readily taken up by cells and is able to participate in redox cycling reactions resulting in the formation of harmful reactive oxygen species [15, 16]. Deferasirox doses ≥ 20 mg/kg/day provided sustained reduction in LPI levels and may therefore contribute to a reduction in unregulated tissue iron loading [17, 18].

Long-term data are critical for the evaluation of iron chelation therapy in patients with β -thalassemia due to the chronic nature of the disease. Median follow-up of patients treated with deferasirox has now been reported in extended phase trials for up to 4.5 years. Results have confirmed that the efficacy of deferasirox depends on both dose and transfusion [19, 20] even in patients unsuccessfully chelated with DFO and/or deferiprone due to unacceptable toxicity, poor response to therapy or non-compliance with treatment regimens [21].

Tolerability and Management of Adverse Events in Patients with β -Thalassemia

The most common drug-related (investigator-assessed) adverse events (AEs) identified in β -thalassemia patients are abdominal pain, nausea, diarrhea, vomiting, and rash; however, the annual frequency of these AEs has generally been shown to decrease from year to year [20]. Such AEs are clinically manageable with regular patient monitoring as the many deferasirox clinical studies have provided information on their onset, severity, duration, and frequency. For diarrhea, patients should be advised to stay hydrated and take an anti-diarrheal for up to 2 days if required. Patients may also benefit from taking deferasirox in the evening rather than the morning or adding products such as Lactaid to their diet [22]. Mild-to-moderate skin rashes are likely to resolve spontaneously; however, severe cases may require dose interruptions and/or adjustments [22]. Non-progressive increases in serum creatinine (rising above the mean of measurements before treatment by $>33\%$ on two consecutive occasions) have been observed in approximately one third of patients treated with deferasirox [8]. However, these increases were dose dependent and often resolved spontaneously. It is recommended that serum creatinine levels are assessed in duplicate before therapy begins and monthly thereafter with any significant increases managed by dose reductions and/or interruptions [22, 23].

Patient Preferences

Compliance with iron chelation therapy is an important issue for patients, as with many chronic conditions. Patients need to be educated about the risks of iron overload and the benefits of remaining compliant with therapy. As deferasirox is an oral therapy, it may be expected that patient compliance would be superior to that seen with DFO infusions [6]. Assessment of patient preferences demonstrated satisfaction and convenience with deferasirox therapy as compared with DFO, with 97% of patients with β -thalassemia who switched to deferasirox from DFO preferring deferasirox. Patients preferred deferasirox due to convenience (37%), absence of injection site soreness (25%) and less disruption to their day (23%) [24]. Greater satisfaction and convenience with deferasirox may translate into improvements in patient compliance and increased effectiveness of chelation therapy.

Deferasirox Therapy in Pediatric Patients with β -Thalassemia

The efficacy and safety of deferasirox have been evaluated in pediatric β -thalassemia patients as young as 2 years of age. The pharmacokinetic profile of deferasirox in pediatric patients (aged 2–7 years) also supports a once-daily dosing regimen; however, the steady-state exposure to deferasirox in children and adolescents is ~ 20 –30% lower than in adults [4, 9]. A conservative dosing strategy was used in preliminary trials in children resulting in an overall gradual increase in LIC [9]; 10 mg/kg/day was used irrespective of the degree of iron overload at baseline with dose adjustments allowed only after 12 weeks of treatment. Longer-term follow-up data in pediatric patients treated with deferasirox for up to 5 years have now demonstrated a dose-dependent reduction in iron burden [25, 26].

The safety profile of deferasirox in pediatric patients is similar to that of adult patients during the 5-year follow-up at doses of up to 30 mg/kg/day [25, 26]. The recommended starting dose and dosing modifications are the same for pediatric and adult patients [23]. To date, neither progressive renal, hepatic, or bone marrow dysfunctions nor deferasirox-induced negative impacts on growth and sexual development have been reported [26].

Deferasirox Therapy in β -Thalassemia Patients with Cardiac Siderosis

Iron-induced cardiac failure and arrhythmia are responsible for as many as 71% of deaths in patients with

Fig. 2. Deferasirox is effective in reducing serum ferritin and LIC across a range of transfusion-dependent anemias. Other anemias include AA (n = 5), α -thalassemia (n = 3), sideroblastic anemia (n = 3), myelofibrosis (n = 2), pure red cell aplasia (n = 2), pyruvate kinase deficiency (n = 2), autoimmune hemolytic anemia (n = 1), Fanconi's anemia (n = 1), hereditary sideroblastic anemia (n = 1), erythropenia (n = 1), and unspecified anemia (n = 1). DW = Dry weight.

β -thalassemia major [1, 27]. The ability of deferasirox to remove iron from the heart is therefore of particular interest. Initial studies in animal models demonstrating the efficacy of deferasirox to reduce cardiac iron content [28] were followed by clinical data to support the effi-

cacy of deferasirox in the removal of cardiac iron and prevention of myocardial siderosis in patients with β -thalassemia major [29–32]. After 1 year of deferasirox treatment (mean dose: 32.6 mg/kg/day) in 114 patients with baseline myocardial T2* of 20 ms (indicative of cardiac iron accumulation), myocardial T2* was shown to improve significantly from a geometric mean baseline of 11.2 to 12.9 ms while left ventricular ejection fraction was maintained at ~67% [30]. In a cohort of 78 patients with normal myocardial iron levels (T2* >20 ms), myocardial T2* was maintained after treatment with deferasirox for 1 year (32.0 ms at baseline and 32.5 ms after 12 months of therapy at a mean dose of 27.6 mg/kg/day), left ventricular ejection fraction significantly increased from 67.7 to 69.6% (p < 0.0001) and body iron burden as assessed by serum ferritin and LIC were significantly reduced [32].

Iron Chelation Therapy in Patients with Thalassemia Intermedia

Defects in the β -globin gene may also result in a diagnosis of β -thalassemia intermedia, which has a wide clinical spectrum with patients often remaining asymptomatic until adult life [33]. In contrast to patients with β -thalassemia major, thalassemia intermedia patients are rarely transfusion dependent; however, they are susceptible to gradual iron overload through increased intestinal absorption of iron secondarily due to chronic anemia and decreased serum hepcidin caused by GDF15 overexpression, which may be exacerbated by occasional blood transfusions. Therefore patients need to be assessed for iron overload. Cardiac iron loading appears to be less of an issue in patients with thalassemia intermedia [34]; however, iron overload should still be monitored in both the liver and the heart. As the clinical consequences of iron overload in thalassemia intermedia are the same as in transfused patients with β -thalassemia major, patients may benefit from iron chelation therapy. Few studies have assessed chelation therapy in thalassemia intermedia [35, 36]; however, there is an ongoing 1-year trial of deferasirox in >150 patients with thalassemia intermedia, representing the first large-scale study of an iron-chelating agent in this patient population.

Myelodysplastic Syndromes

MDS is a group of heterogeneous disorders characterized by impaired blood cell production by the bone marrow. Managing MDS is often complicated by the gener-

Table 1. Efficacy of deferasirox across a variety of transfusion-dependent anemias included in the EPIC trial

	All patients (n = 1,744) [7]	β -Thalassemia major (n = 937) [13]	MDS (n = 341) [43]	AA (n = 116) [45]	Rare anemias (n = 43) [46]	DBA (n = 14) [47]
Baseline serum ferritin, ng/ml	3,135	3,157	2,730	3,254	3,161	2,289
Median change in serum ferritin, ng/ml	-264	-129	-253	-964	-832	-790
p value	<0.0001	0.0007	0.0019	0.0003	0.0275	0.0121
Average deferasirox dose during study, mg/kg/day	22.2	24.2	19.2	17.6	18.6	21.0

ally advanced age of patients (median age 65–70 years) [37]. Red blood cell transfusions are the mainstay of supportive care for MDS [38] and up to 90% of MDS patients with chronic anemia become dependent on transfusions to manage the symptoms of anemia [38]; however, blood transfusion therapy is associated with increased risk of iron toxicity. Chelation therapy is recommended by several treatment guidelines in patients who have an International prognostic Scoring System risk of low or intermediate-1 and serum ferritin levels of >1,000–2,000 ng/ml, depending on transfusion requirements [37, 39, 40]. Response to chelation therapy may not be the same as in β -thalassemia patients due to differences in the magnitude of directly chelatable iron pools, and thus specific data are required to evaluate efficacy and safety [5]. There are a limited number of small-scale studies on the use of DFO and deferiprone in this patient population; however, several larger clinical trials with deferasirox have provided more robust data [5, 41–43].

Deferasirox Therapy in Patients with MDS

Deferasirox has been shown to maintain or reduce body iron in patients with MDS in several clinical trials [5, 42–44]. In one study of 176 patients, deferasirox decreased mean serum ferritin over 1 year and normalized LPI levels [42]. In another study comparing responses to iron chelation among various disease groups, a similar pattern of dose-dependent iron excretion was observed in patients with MDS compared with β -thalassemia (fig. 2) [5]. More recently, the EPIC trial enrolled the largest cohort of MDS patients to date (n = 341). Despite a high transfusion requirement and iron burden in this cohort, almost 50% had received no prior chelation therapy. Deferasirox provided significant reduction in serum ferritin over the 1-year treatment period with appropriate dose adjustments every 3 months as required (table 1) [7, 13, 43, 45–47]. The most common AEs con-

sidered related to treatment included mild-to-moderate gastrointestinal symptoms consistent with those identified in patients with β -thalassemia. However, the discontinuation rate was higher and investigations are ongoing to determine possible contributing factors such as existing co-morbidities and the advanced age of this patient subgroup [43].

Sickle Cell Disease

SCD is a group of inherited disorders caused by the sickle mutation affecting the β -globin chain of hemoglobin. Erythrocytes containing hemoglobin S have irregular morphology and under low oxygen conditions, hemoglobin S polymerizes leading to ‘sickled’ cells [48]. The pathogenesis of SCD relates to the shortened lifespan of the sickled erythrocytes (16–20 days in contrast to a lifespan of 120 days for normal erythrocytes) and adhesion of the sickled erythrocytes to the microvascular endothelium. Transfusion of red blood cells on a chronic or intermittent basis is therefore important in the management of SCD. There is increasing evidence of the value of transfusions particularly in reducing the risk of stroke in pediatric patients with SCD [49, 50]. However, progressive iron loading and tissue injury as a result of frequent blood transfusions appear to be similar to those in other transfusion populations [51].

Deferasirox Therapy in Patients with SCD

In comparison with DFO, deferasirox has been shown to have similar efficacy and a well-defined, manageable safety profile in both adult and pediatric patients (aged 3–54 years) with SCD [6]. After 1 year of treatment with deferasirox (10–30 mg/kg/day), LIC was significantly reduced compared with baseline ($p < 0.05$) and serum ferritin was also decreased, although with inpatient vari-

ability. The incidence of AEs including sickle cell crisis was also similar in both groups (46.2% with deferasirox and 42.9% with DFO) [6]. As part of this phase II study, patient-reported outcomes were also evaluated. Throughout the study, significantly more patients receiving deferasirox reported being 'satisfied' or 'very satisfied' with treatment compared with those on DFO ($p < 0.001$) [52]. Similar outcomes were also reported regarding convenience of deferasirox therapy. Cumulative 3.5-year data of deferasirox in SCD patients have now demonstrated continued reduction in body iron (based on serum ferritin levels) without any exposure-associated increased risk of AEs, renal dysfunction, or progressive increases in serum creatinine [53].

Other Rare Anemias

Deferasirox Therapy in Patients with DBA

DBA is a rare type of congenital erythroid aplasia that occurs in 5–10 of every 1 million births, where anemia occurs due to the failure of erythropoiesis [54]. In a 1-year study of deferasirox in patients with DBA, doses of 20 and 30 mg/kg/day induced a negative iron balance in a similar pattern to patients with other underlying anemias such as β -thalassemia and MDS (fig. 1; $n = 30$) [5]. These data were supported by results from the prospective EPIC trial, where a significant reduction in serum ferritin from baseline was observed in patients with DBA receiving an average daily dose of ≥ 20 – <30 mg/kg/day ($-1,095.0$ ng/ml; $p = 0.0015$; table 1) [47]. The majority of DBA patients (86%) in the EPIC trial had received prior chelation therapy with DFO and/or deferiprone; however, median baseline serum ferritin was still elevated. The AE profile was similar to that observed in other patient groups [5, 47].

Deferasirox Therapy in Patients with AA

AA often results from other bone marrow disorders (such as MDS) as a result of complete bone marrow failure. The worldwide annual incidence is estimated at 2 of every 1,000,000 births [55]. AA can be treated with bone marrow transplantation or immunosuppressive therapy; however, the main supportive therapy involves regular blood transfusions [56]. Over a 1-year treatment period, deferasirox significantly reduced iron burden in patients with AA at an average actual dose of 17.6 ± 4.8 mg/kg/day (table 1) [45]. Interestingly, 68% of AA patients enrolled in this trial had received no prior treatment with chelation therapy even though they had an elevated median serum ferritin at baseline (3,254 ng/ml) associated

with significant negative outcomes [1], thereby indicating a need for iron chelation therapy in this patient population [45]. Deferasirox was generally well tolerated, with the most common ($>10\%$) drug-related AEs including nausea, diarrhea, and rash; most AEs ($>95\%$) were of mild-to-moderate severity.

Future Developments

To date, the deferasirox clinical development program has focused on the treatment of patients with transfusional iron overload; however, a wider perspective is now being taken with the investigation of deferasirox in a number of other conditions including hereditary hemochromatosis (HH; characterized by progressive iron overloading through increased intestinal absorption [57]), chronic hepatitis C [58], porphyria cutanea tarda (a common type of porphyria which can be associated with hemochromatosis [59]), and mucormycosis.

Phlebotomy is the standard of care in HH patients to reduce serum ferritin levels and prevent clinical complications of iron overload. However, compliance with phlebotomy tends to decrease with time due to the inconvenience of frequent clinic visits and discomfort of the procedure; some patients may also be poor candidates due to underlying medical disorders and/or poor venous access. A study is ongoing to evaluate the safety and efficacy of deferasirox as a further treatment option in patients with HH (adult patients homozygous for the C282Y mutation) [60] and preliminary results suggest that deferasirox doses of 5, 10 and 15 mg/kg/day are effective at reducing iron burden with an acceptable safety profile [61]. Preliminary studies in the treatment of chronic hepatitis C infection with interferon/ribavirin have suggested that previous treatment with deferasirox may improve early viral response rates [58]. A pilot trial to investigate the efficacy and tolerability of deferasirox in the treatment of porphyria cutanea tarda is currently recruiting patients (ClinicalTrials.gov identifier: NCT00599326). Deferasirox has also been shown to significantly improve survival and decrease tissue fungal burden in mice infected with mucormycosis [62]. A clinical study to determine whether the addition of deferasirox to standard antifungal therapy, liposomal amphotericin B (LAmB; AmBisome), is safe and effective for the treatment of mucormycosis is also currently recruiting patients (DEFEAT Mucor study; ClinicalTrials.gov identifier: NCT00419770).

Additionally, the benefits of reduced iron levels in bone marrow transplant patients before and after trans-

plantation have been recognized [63] and, therefore, deferasirox also has a potential application in this patient population.

Conclusions

Long-term red blood cell transfusions are required for the treatment of many anemias including β -thalassemia, MDS, SCD, DBA, and AA. Frequent transfusions inevitably lead to iron overload, which has serious clinical sequelae. The oral iron chelator deferasirox has been evaluated in heterogeneous populations of patients with a variety of underlying anemias demonstrating consistent efficacy and safety profiles. The results from the large-scale EPIC trial and data from long-term studies further

support these observations as well as the importance of timely dose adjustments based on serum ferritin trends to adapt therapy for individual patients. Emerging data on the cardiac efficacy of deferasirox are also encouraging in both the prevention and treatment of cardiac iron accumulation. Deferasirox therefore represents a significant advance in the treatment of a wide variety of patients with chronic iron overload, with further potential applications still to be explored.

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