Optimising management of deferasirox therapy for patients with transfusion-dependent thalassaemia and lower-risk myelodysplastic syndromes

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Abstract
Effective iron chelation therapy is an important part of treatment in patients with transfusion-dependent thalassaemia and lower-risk myelodysplastic syndromes (MDS). Key strategies for optimising iron chelation therapy include ensuring good adherence and preventing and managing adverse events (AEs). Good adherence to iron chelation therapy with deferoxamine and deferasirox has been linked to improved survival and/or reductions in complications related to iron overload; however, maintaining good adherence to iron chelators can be challenging. Patients with transfusion-dependent thalassaemia or lower-risk MDS showed better adherence to the deferasirox film-coated tablet (FCT) formulation than to the deferasirox dispersible tablet formulation in the ECLIPSE trial, reflecting in part the improved palatability and convenience of deferasirox FCT. As well as affecting adherence, AEs may lead to dose reduction, interruption or discontinuation, resulting in suboptimal iron chelation therapy. Preventing and successfully managing AEs may help limit their impact on adherence, and following dosage and administration recommendations for iron chelators such as deferasirox may help minimise AEs and optimise treatment in patients with transfusion-dependent thalassaemia and lower-risk MDS.

KEYWORDS
deferasirox, iron overload, myelodysplastic syndromes, thalassaemia, therapy

1 | INTRODUCTION

Iron overload is a consequence of red blood cell (RBC) transfusion in patients with refractory anaemias who require ongoing transfusion support, including patients with transfusion-dependent thalassaemia and myelodysplastic syndromes (MDS).1,2 In the long-term, untreated transfusional iron overload results in complications such as cardiac dysfunction, hepatic dysfunction and failure, and endocrinopathies.1 Iron chelation therapy decreases the iron burden, thereby preventing and/or delaying long-term complications associated with iron deposition in tissues.1,2

Currently available iron chelators include parenteral deferoxamine and oral formulations of deferiprone (tablet and oral solution) and deferasirox, including deferasirox dispersible tablets (deferasirox DT) and a film-coated tablet formulation of deferasirox (deferasirox FCT). Deferoxamine is administered by slow subcutaneous or intravenous infusion 5–7 times weekly.2 Deferiprone is administered 3 times daily,6 and deferasirox DT and deferasirox FCT are administered once daily.2,10 Other properties of these iron chelators are summarised in Table 1. A granule formulation of deferasirox is also available in some countries10; this granule formulation is particularly intended for use in paediatric patients and has similar properties to deferasirox FCT.

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Factors to consider when selecting an iron chelator include iron burden, patient preference, tolerability and adherence. A suggested approach to optimising iron chelator therapy in patients with transfusion-dependent thalassaemia and high iron stores when magnetic resonance imaging (MRI) results are available is shown in Figure 1. Patients with satisfactory iron stores (serum ferritin consistently 500-1500 μg/L and liver iron concentration [LIC] 3-7 mg Fe/g dry weight [dw]) and myocardial T2* (>20 milliseconds) can continue their current iron chelator regimen or be offered deferasirox if their current regimen is not tolerated or associated with poor adherence, or if they request a change. The iron chelator dose should be reduced or treatment should be interrupted in patients with rapidly decreasing or low iron stores (ie, serum ferritin consistently <1000 μg/L and LIC <3 mg Fe/g dw). If MRI is not available, it is recommended that serial serum ferritin levels should be obtained every 3 months and used to monitor iron overload.

The efficacy of deferasirox DT in patients with transfusion-dependent thalassaemia and iron overload is well established. Median serum ferritin levels (primary endpoint) were significantly reduced from baseline in the prospective, multinational, 1-year phase IIIb EPIC trial, in which 1744 patients with transfusional iron overload (1115 [64%] of whom had transfusion-dependent thalassaemia) received fixed starting doses of deferasirox DT (20 mg/kg/day in patients receiving 2-4 packed RBC units per month, with 10 or 30 mg/kg/day recommended in patients receiving less or more frequent RBC transfusions, respectively). Deferasirox DT also removed myocardial iron and prevented myocardial iron accumulation in patients with transfusion-dependent thalassaemia in the EPIC cardiac substudy. In the EPIC liver substudy, deferasirox DT at a mean actual dose ≈20 mg/kg/day maintained LICs in patients with a baseline LIC of <7 mg Fe/g dw, while deferasirox DT at a mean actual dose ≈30 mg/kg/day significantly reduced LIC in patients with a baseline LIC of ≥7 mg Fe/g dw.

Data from other studies also support the efficacy of deferasirox DT in patients with transfusion-dependent thalassaemia (n = 71-237). For example, deferasirox was noninferior to deferoxamine in terms of reducing myocardial iron in the CORDELIA trial, and stabilised or improved liver fibrosis in another study. Combination therapy with deferasirox and deferiprone has also demonstrated potential in patients with transfusion-dependent thalassaemia and iron overload. In the HYPERION trial, the combination of deferasirox and deferiprone in patients with severe transfusional myocardial siderosis improved mT2* and rapidly reduced liver iron.

### Table 1: Properties of iron chelators used in patients with transfusion-dependent thalassaemia or lower-risk MDS and iron overload

|                        | Deferoxamine | Deferiprone | Deferasirox |
|------------------------|--------------|-------------|-------------|
| **Route of administration** | Slow SC or IV infusion | Oral | Oral |
| **Schedule** | 5-7 times weekly | 3 times daily | Once daily |
| **Usual starting dose** | SC: 20-60 mg/kg/d over 8-24 h; IV: 20-40 mg/kg/d (children) or 40-50 mg/kg/d (adults) over 8-12 h | 75 mg/kg/d | 20 mg/kg/d |
| **Maximum dose** | 100 mg/kg/d | 40 mg/kg | 28 mg/kg |
| **Tablet strengths** | 500, 1000 mg | 125, 250, 500 mg | 90, 180, 360 mg |
| **Oral solution** | 50 g/500 mL |  |  |
| **Excretion** | Urinary, with some faecal excretion | Mainly urinary | Mainly faecal |
| **AEs** | Injection-site reactions, high-frequency hearing loss, retinopathy, *Yersinia* infection, poor growth | GI AEs (nausea, vomiting, abdominal pain), increased ALT levels, arthralgia, neutropenia | GI AEs (diarrhoea, vomiting, nausea, abdominal pain), rash, increased ALT levels, increased serum creatinine, proteinuria |
| **Warnings** | Agranulocytosis, neutropenia | Renal toxicity, hepatic toxicity, GI haemorrhage | Renal toxicity, hepatic toxicity, GI haemorrhage |

AE, adverse event; ALT, alanine aminotransferase; GI, gastrointestinal; IV, intravenous; MDS, myelodysplastic syndromes; SC, subcutaneous.

*aDoes not contain lactose and sodium lauryl sulphate excipients, may be taken with a light meal, can be swallowed whole with no preparation or mixing required or may be crushed and sprinkled onto soft food.*
with MDS (n = 341) included in the EPIC trial, deferasirox DT significantly (P < .01) reduced serum ferritin levels and labile plasma iron (LPI) from baseline, with a significant correlation (P < .0001) seen between the reduction in serum ferritin levels and the improvement in alanine aminotransferase (ALT) levels, an indicator of hepatocellular injury. Other prospective studies that included patients with lower-risk MDS and transfusional iron overload (n = 24-173) demonstrated significant (P < .05) reductions from baseline in serum ferritin levels and LIC with deferasirox DT, and normalisation or stabilisation of LPI levels.

In terms of survival outcomes, retrospective analyses suggested significantly (P < .05) improved survival in different cohorts of patients (n = 78-263) with predominantly lower-risk MDS who received iron chelation therapy (predominantly deferoxamine or deferasirox) compared with those who did not.

Worse health-related quality of life (HRQoL) was seen in patients with thalassaemia and MDS in the EPIC trial, when compared with age-matched norms derived from the UK general population. In EPIC, deferasirox DT was associated with improvements in HRQoL in patients with thalassaemia, but not in patients with MDS. HRQoL also remained stable over time in 152 patients with transfusion-dependent lower-risk MDS who received deferasirox DT.

Patient-reported satisfaction with iron chelator-related adverse effects, acceptance and burden improved with deferasirox DT therapy in both patients with thalassaemia and those with MDS in the EPIC trial.

This article discusses the importance of optimising iron chelation therapy in patients with transfusion-dependent thalassaemia or lower-risk MDS and strategies for optimising the use of deferasirox with a focus on adherence and safety.

## 2 | ADHERENCE TO IRON CHELATION THERAPY

### 2.1 | Importance of adherence

Methods of measuring iron chelator adherence include self-reported medication use (assessed using questionnaires) and more objective measures such as pill counts and prescription refills. Serum ferritin levels, LIC, and signs of iron overload may also be used to assess adherence in patients with transfusion-dependent thalassaemia or MDS. Self-reporting may overestimate adherence, with self-reported iron chelator adherence in adolescents with thalassaemia seemingly higher than adherence indicated by serum ferritin levels. Indeed, adolescents pose particular challenges in terms of both evaluating adherence (with the reliability of information improved when it comes from multiple sources such as the adolescent, their parents, and healthcare providers).
and maintaining adherence.39 Among patients with thalassaemia, the highest rates of adherence to iron chelator therapy have been reported in children (most likely reflecting parental supervision) and older adults.40

The toxicity of iron overload takes a long time to manifest and is not appreciated promptly by patients. Given that many patients with transfusion-dependent anaemias require lifelong transfusions and iron chelation therapy, maintaining adherence to treatment can be challenging.41 However, maintaining adherence to iron chelation therapy is essential for controlling iron burden and thus improving survival and reducing iron toxicity-associated morbidity.

Iron chelation therapy had greater efficacy, as assessed by serum ferritin levels, in patients who were adherent to treatment.42,43 For example, in a retrospective observational study in patients with MDS and transfusional iron overload (n = 35), patients who adhered to treatment with deferasirox achieved significantly lower median serum ferritin levels (1204 [interquartile range (IQR) 567-1652] vs 1430 [IQR 955-1815] μg/L; P = .016), and a significant inverse correlation (r = −0.288; P = .004) was seen between adherence to deferasirox DT and serum ferritin levels.42

The frequency and severity of complications related to iron overload are also influenced by adherence to iron chelators.41 In patients with transfusion-dependent thalassaemia, poor adherence to deferoxamine therapy was associated with an increased risk of cardiac disease and death.42-46

Adherence to deferasirox DT of <90% was associated with a decrease in mT2*, while compliance of ≥90% was associated with an increase in mT2* (P = .0001) in patients with transfusion-dependent thalassaemia or rare anaemias (n = 33) who received deferasirox DT for up to 4 years.47

### 2.2 | Adherence rates

Results of comparative trials suggest that adherence rates are lower with the parenteral iron chelator deferoxamine than with the oral iron chelators deferiprone41 or deferasirox DT.48,49 In one study, self-reported adherence was significantly lower among 171 patients receiving deferoxamine than among 494 patients receiving deferasirox (92% vs 96%; P < .001), and a significant (P = .03) improvement in adherence was reported among patients who switched from deferoxamine to deferasirox.49 Of 21 patients receiving deferoxamine and 75 patients receiving deferasirox DT in a second study, only 10% and 33% of patients, respectively, reported that they always adhered to treatment.50

Among patients with a prior history of iron chelation therapy in the EPIC trial, the proportion of patients with transfusion-dependent thalassaemia who reported always following their iron chelation therapy regimen as recommended by their physician increased from 58 of 179 (32%) patients at baseline to 116 of 173 (67%) patients at end of study (ie, after 1 year’s therapy with deferasirox DT or at the time of early discontinuation).35 In patients with MDS, adherence was reported by 35 of 56 (63%) patients at baseline and 36 of 42 (86%) patients at end of study.35

Discontinuation rates (used as a surrogate of adherence) appear lower in patients with thalassaemia than in those with MDS. For example, in the EPIC trial, 9% of patients with thalassaemia and 49% of patients with MDS had discontinued deferasirox DT therapy at 1 year.15 In prospective observational studies (eXtend and eXjange) in patients with MDS and iron overload, 62% of chelation-naïve patients in eXtend (n = 123) and 71% of prechelated patients in eXjange (n = 44) were still receiving deferasirox DT at 1 year.50

In the retrospective study in patients with MDS and transfusional iron overload who received deferasirox DT for a median IQR duration of 11.0 (IQR 3.0-37.8) months, the median adherence rate during treatment was 92%.42 Adherence was measured using the medication possession ratio (MPR) and patients were considered adherent when the MPR was ≥90%. Only 55% of patients had an adherence rate of ≥90% at every follow-up measurement during the whole duration of treatment.42

Adherence to iron chelation therapy may decrease over time. In patients with transfusion-dependent thalassaemia or rare anaemias who received deferasirox DT for up to 4 years, the proportion of patients achieving ≥90% self-reported adherence decreased from 90% in the first year of treatment to 69% in the fourth year of treatment.47

### 3 | BARRIERS TO ACHIEVING ADHERENCE AND OPTIMAL IRON CHELATION THERAPY

#### 3.1 | Factors affecting adherence

Various factors may affect adherence to iron chelation therapy, most of which are related to the characteristics of the chelator, such as the mode of administration, dose schedule, and adverse events (AEs).

Mode of administration is probably the main factor affecting adherence, with oral iron chelator formulations generally preferred over parenteral iron chelator formulations. Patients with transfusion-dependent thalassaemia enrolled in a prospective nonrandomised study reported that deferasirox (n = 75) had less negative impact than deferoxamine (n = 21) on HRQoL, the ability to perform daily tasks, and body and skin appearance, which are all factors that may impact adherence.48

In a multinational study, over 40% of patients receiving deferoxamine infusions (n = 79) reported problems at least sometimes with sticking themselves or with wearing the pump, and patients with poor adherence to deferoxamine also reported issues such as the infusions being painful and the injection site being sore, saturated or leaking.40

Convenience and administration frequency may affect adherence. Deferasirox tablets have a convenient once-daily oral administration regimen.2,51 In a Phase III, noninferiority trial in patients with transfusion-dependent thalassaemia and iron overload who received deferasirox and deferoxamine (n = 586),52 patient-reported satisfaction and convenience were significantly (P < .001) higher with deferasirox DT than with deferoxamine.53

However, adherence to deferasirox DT may be affected by the requirement to take it in a fasting state,7,8 as when taken with food,
the bioavailability of deferasirox DT is affected by the type, the caloric content, and the fat content of the meal.\textsuperscript{54} When deferasirox DT is administered with food, drug exposure increased as the fat content of the meal increased.\textsuperscript{54} These findings led to the recommendation that deferasirox DT be administered ≥30 minutes before a meal.\textsuperscript{7,8} Although administering deferasirox DT in the fasting state with a limited range of beverages may prevent beverage- and food-related fluctuations in drug absorption, it may prove onerous to patients resulting in poor adherence.\textsuperscript{55}

Adherence to deferasirox DT is also affected by palatability issues.\textsuperscript{40,55} When the palatability of deferasirox DT, administered according to the label (ie, deferasirox DT administered 30 minutes before a meal and dispersed in water, apple juice, or orange juice), was rated, 37.8% of patients liked deferasirox DT, 23.8% neither liked nor disliked deferasirox DT, and 35.1% disliked deferasirox DT.\textsuperscript{55} The highest palatability rating was seen when deferasirox DT was taken with soft food at breakfast.\textsuperscript{55}

### 3.2 Adverse events

As well as affecting adherence, AEs may lead to dose reduction, interruption, or discontinuation, resulting in suboptimal iron chelation therapy. In the EPIC trial, the deferasirox DT dose was reduced, treatment was interrupted, or treatment was discontinued because of AEs, particularly gastrointestinal (GI) AEs, and/or laboratory abnormalities in 11.4%, 24.4%, and 8.8% of patients, respectively.\textsuperscript{36}

The most commonly reported AEs in patients receiving deferasirox DT included GI AEs and rash.\textsuperscript{15,25,52} More specifically, in the EPIC trial they included abdominal pain (4.8% of patients with transfusion-dependent thalassaemia and 7.6% of patients with MDS), nausea (3.8% and 13.2%), vomiting (1.8% and 7.6%), diarrhoea (7.8% and 32.6%), and rash (11.5% and 6.7%).\textsuperscript{15,25} There was a higher risk of GI AEs in patients with a baseline LIC of <7 mg Fe/g dw.\textsuperscript{17} Most drug-related AEs were of mild-to-moderate severity and rarely required discontinuation of treatment (1.3% and 0.5% of patients due to rash or diarrhoea, respectively).\textsuperscript{15,25}

Increases in serum creatinine levels (which were generally mild, nonprogressive, and reversible) have been reported in patients receiving deferasirox.\textsuperscript{15,25,52,56,57} Over 1 year of follow-up in the EPIC trial, 2 consecutive increases in serum creatinine of >33% above baseline and exceeding the upper limit of normal (ULN) occurred in 3.6% of patients with transfusion-dependent thalassaemia\textsuperscript{15} and in 25% of patients with MDS.\textsuperscript{25} Deferasirox dose reductions, interruptions, and discontinuations because of increased serum creatinine levels occurred in 33.1%, 10.9%, and 1.7% of patients, respectively, in the overall study population,\textsuperscript{15} and in 10.0%, 2.6%, and 0.3% of patients, respectively, in the MDS subgroup.\textsuperscript{25} Nevertheless, increases in serum creatinine observed in the longer term (up to 5 years’ follow-up) were generally mild and nonprogressive, with median serum creatinine levels remaining within the normal range.\textsuperscript{56}

Proteinuria has also been reported in patients receiving deferasirox.\textsuperscript{15} Drug-related proteinuria was reported in 0.6% of patients over 1 year of follow-up in the EPIC trial.\textsuperscript{15}

Hepatic injury has been reported in some patients receiving deferasirox.\textsuperscript{7,10} Over 1 year of follow-up in the EPIC trial, 2 consecutive increases in ALT levels of >10 × ULN were reported in 0.6% of patients with transfusion-dependent thalassaemia and in 0.3% of patients in the MDS subgroup.\textsuperscript{15}

There have been rare reports of renal tubular damage (including Fanconi’s syndrome), acute renal failure, hepatic failure, visual abnormalities (eg, lens opacities), auditory abnormalities (eg, hearing loss), and GI haemorrhage in patients receiving deferasirox DT.\textsuperscript{15,25,58}

### 4 Strategies for Improving Adherence and Optimising Deferasirox Therapy

#### 4.1 Changes to the deferasirox formulation

In an attempt to tackle the adherence barriers related to palatability and convenience, the deferasirox FCT formulation was developed. Deferasirox DT is recommended to be taken on an empty stomach (≥30 minutes before the next meal), its administration requires complete dispersion of the tablets in a glass of water, orange juice, or apple juice, and the suspension has a chalky consistency.\textsuperscript{7,8} while deferasirox FCT can be swallowed whole or crushed, and can be taken on an empty stomach or with a light meal (defined as a meal containing <7% fat content and ±250 calories).\textsuperscript{7,10}

Deferasirox FCT has 36% greater bioavailability than deferasirox DT and, thus, the dose of deferasirox FCT required to achieve the same chelation effect as deferasirox DT is =30% lower.\textsuperscript{7,10} Exposure may increase further (up to 18%) if deferasirox FCT is taken with a high-fat meal.\textsuperscript{10} In addition, while deferasirox FCT contains the same active substance as deferasirox DT, some of the excipients (lactose and sodium lauryl sulphate) have been removed.\textsuperscript{7,10}

The 24-week, Phase II, randomised, open-label ECLIPSE study compared the deferasirox DT and FCT formulations in patients with transfusion-dependent thalassaemia or very low-, low-, or intermediate-risk MDS.\textsuperscript{59} At least 12 weeks’ therapy was completed by 96.6% of patients receiving deferasirox FCT and 89.5% of patients receiving deferasirox DT. No new safety signals were seen with deferasirox FCT. All-cause AEs occurred in 89.5% of deferasirox DT recipients and 89.7% of deferasirox FCT recipients, with severe AEs occurring in 25.6% and 19.5% of patients in the corresponding treatment groups.\textsuperscript{59}

In the same trial, patients receiving deferasirox FCT experienced a lower exposure-adjusted GI AE rate than those receiving deferasirox DT (137 vs 153 per 100 patient-years), although the overall incidence of GI AEs was similar (58.6% vs 61.6% of patients).\textsuperscript{59} Severe GI AEs were reported in 4.6% of deferasirox FCT recipients and 12.8% of deferasirox DT recipients. Renal events (ie, renal AEs and abnormal renal laboratory parameters) occurred in 33 patients receiving deferasirox FCT and in 26 patients receiving deferasirox DT. Post hoc analysis found that 10 of the 33 (30.3%) deferasirox FCT recipients and 4 of the 26 (15.4%) deferasirox DT recipients who experienced renal events started treatment on a higher than recommended dose
of deferasirox. Renal AEs were reported in 20 of 60 (33.3%) patients receiving deferasirox FCT and in 21 of 68 (30.9%) patients receiving deferasirox DT at the correct starting dose.59

Treatment adherence (assessed by tablet count) was 92.9% in patients receiving deferasirox FCT and 85.3% in patients receiving deferasirox DT.59 In ECLIPSE, clinically significant differences were seen between patients receiving deferasirox FCT and those receiving deferasirox DT in terms of patient-reported outcomes.59 Consistently better adherence and satisfaction/preference, and consistently fewer concerns were reported with deferasirox FCT than with deferasirox DT. Patients in both treatment arms experienced very little trouble/concern associated with GI AEs.59 Patients consistently found deferasirox FCT more palatable than deferasirox DT.59 Patients receiving deferasirox FCT reported no aftertaste and were more likely than those receiving deferasirox DT to report that they were able to swallow the full amount of medicine with the right amount of liquid.59

4.2 | Optimise deferasirox dose and administration

It is important to start patients on the correct dose of deferasirox to optimise treatment and minimise AEs and laboratory abnormalities (Table 2). The usual starting dose recommended for patients aged ≥2 years with transfusional iron overload is deferasirox DT 20 mg/kg once daily, or deferasirox FCT 14 mg/kg once daily.7-10 A reduced starting dose of deferasirox is recommended in patients with moderate hepatic impairment or creatinine clearance (CL_{Cr}) of 40-60 mL/min. Deferasirox use should be avoided in patients with severe hepatic impairment and is contraindicated in patients with CL_{Cr} <40 mL/min or serum creatinine >2 × the age-appropriate ULN.7-10

During therapy, deferasirox dose adjustments should be made based on serum ferritin levels (Table 2).7-10 There is potential for drug interactions between deferasirox and certain other medications, including aluminium-containing antacid preparations, substrates of cytochrome P450 (CYP) 3A4, CYP2C8 and CYP1A2, inducers of UDP-glucuronosyltransferase, and bile acid sequestrants.7-10 Recommendations for avoiding drug interactions are summarised in Table 2.

4.3 | Management of AEs

Taking measures to prevent AEs and appropriately managing AEs and laboratory abnormalities when they occur may also help improve adherence to deferasirox. In terms of preventing GI AEs, the potential of concomitant medications to cause gastric or duodenal ulceration should be evaluated, with special consideration given to nonsteroidal anti-inflammatory drugs.51,58 Monitoring recommendations and strategies for managing AEs in patients receiving deferasirox DT and deferasirox FCT are outlined in Table 3.7-10,51,58

Serum creatinine and transaminase levels should be monitored during deferasirox therapy (Table 3). Dose reduction, interruption, or discontinuation of deferasirox may be needed depending on the extent of the increase in serum creatinine levels.7-10 Increased transaminase levels may relate to iron load rather than deferasirox therapy, although dose modification or interruption of deferasirox may be needed for severe or persistent transaminase elevations.7-10,60

Suggested management strategies for transaminase elevations, based on the authors’ clinical experience and taking into account LICs, are shown in Table 4.

As mentioned previously, the GI tolerability of deferasirox FCT appears better than that of deferasirox DT. Various measures can be used to help manage GI AEs (Table 3). For example, administering deferasirox at a particular time of day (eg, preprandial evening dosing) may help ameliorate GI AEs, and dispersing deferasirox DT in water rather than in apple juice or orange juice may help manage diarrhoea.51,58 Antacids, H₂-receptor antagonists, and proton pump inhibitors can be used to manage GI AEs, although aluminium-containing antacid preparations should be avoided (Table 3).58 Given that deferasirox DT also contains lactose as an excipient, lactase supplementation may be beneficial in patients who experience diarrhoea because of lactose intolerance.58 By contrast, deferasirox FCT does not contain lactose, which may contribute to its improved GI tolerability.

The rash reported in patients receiving deferasirox is characterised as maculopapular, pruritic, and diffuse.58 Rash of mild-to-moderate severity often resolves spontaneously and requires only supportive treatment (Table 3).58 Severe rash may require the interruption of deferasirox therapy and treatment with systemic corticosteroids may be considered.58

5 | DISCUSSION

The benefits of iron chelation therapy in transfusional iron overload are well established in terms of reducing serum ferritin levels and improving long-term morbidity and mortality. Various factors should be considered when selecting an iron chelator, including the iron burden, patient preference, tolerability, and adherence.1

Good adherence to iron chelation therapy with deferoxamine and deferasirox has been linked to improved survival and/or reductions in complications related to iron overload.43-47 However, maintaining good adherence to iron chelation therapy can be challenging, particularly in patients with lifelong transfusion dependency and a lifelong requirement for continuous iron chelation therapy. In an attempt to improve adherence, deferasirox FCT was developed. Indeed, adherence was better with deferasirox FCT than with deferasirox DT in the ECLIPSE trial, as assessed by both pill count and patients’ reports.59 Factors that may have contributed to better adherence include the improved palatability and convenience of the deferasirox FCT formulation. The deferasirox FCT formulation can be swallowed whole with light meals, which may improve patient convenience and satisfaction. As shown in the same trial, higher satisfaction/preference was reported by patients receiving deferasirox FCT vs deferasirox DT.59

Successfully managing AEs may help limit their impact on adherence. Deferoxamine, deferiprone, and deferasirox DT and FCT all
have monitoring requirements for AEs and laboratory abnormalities to help avoid AEs. Any AEs or laboratory abnormalities that emerge during treatment should be managed in accordance with the product labels.

Starting patients on the correct dose of deferasirox DT and deferasirox FCT is also important in terms of minimising AEs and laboratory abnormalities. Post hoc analysis in the ECLIPSE trial demonstrated that of the deferasirox FCT recipients who experienced renal events, one-third started treatment with deferasirox FCT at a higher than recommended dose, which may have an impact on renal...
| Prior to starting therapy |
|---------------------------|
| Measure baseline serum creatinine level in duplicate and calculate CL_{\text{CR}} (Cockcroft-Gault method) |
| Measure proteinuria |
| Measure serum transaminases and bilirubin |
| Conduct baseline auditory and ophthalmic examinations |

**Monitoring recommendations during treatment**

| Serum creatinine | Monitor weekly during the first month after initiation of modification of therapy and at least monthly thereafter |
| Proteinuria | Monitor monthly for proteinuria |
| Serum transaminases and bilirubin | Monitor every 2 wk during the first month of treatment and at least monthly thereafter |
| Auditory/ocular disturbances | Perform auditory and ophthalmic examinations at regular intervals (every 12 mo) Monitor more frequently if disturbances are noted and consider dose reduction or interruption |
| GI ulcer/haemorrhage | Monitor for GI ulcer and haemorrhage during treatment Promptly initiate additional evaluation and treatment if a serious GI AE is suspected |
| Complete blood count | Monitor complete blood count in all patients Interrupt treatment if a patient develops cytopenias until the cause has been determined Contraindicated in patients with platelet counts <50 × 10^9/L |

**Managing increased serum creatinine levels during treatment**

- Patients aged 2-15 y If serum creatinine increases by ≥33% above average baseline measurement and greater than the age-appropriate ULN, reduce the dose by 10 mg/kg (deferasirox DT) or 7 mg/kg (deferasirox FCT)
- Patients aged ≥16 y If serum creatinine increases by ≥33% above average baseline measurement, repeat within 1 wk, and if still elevated by ≥33%, reduce the dose by 10 mg/kg (deferasirox DT) or 7 mg/kg (deferasirox FCT)
- All patients (regardless of age) Discontinue therapy if serum creatinine >2 × age-appropriate ULN or for CL_{\text{CR}} <40 mL/min

**Managing increased transaminase levels during treatment**

Consider dose modification or interruption of treatment for persistent or severe elevations

**Managing rash during treatment**

- Mild-to-moderate rash Often resolves spontaneously; continue treatment without dose adjustment
- Severe rash Interrupt treatment and consider the use of systemic corticosteroids

**Managing diarrhoea during treatment**

- Mild Supportive care including hydration, discontinue use of laxatives/stool softeners, use water to disperse deferasirox DT Consider use of loperamide
- Moderate Use supportive measures and loperamide Temporarily reduce deferasirox dose
- Severe Use supportive measures and loperamide Interrupt deferasirox therapy

**Managing abdominal pain during treatment**

Avoid deferasirox dosing before bedtime
Thus, it is of great importance to be very cautious when patients are switched from deferasirox DT to deferasirox FCT. Not only does the dose of deferasirox FCT need to be 30% less than that of deferasirox DT, but close monitoring is required postswitch, as adherence may significantly improve, affecting the exposure of the iron chelator.

No new safety signals were seen with deferasirox FCT in ECLIPSE. GI AEs are among the most commonly reported AEs in patients receiving deferasirox. It has been suggested that the lactose and sodium lauryl sulphate excipients in deferasirox DT may be implicated in GI AEs and it was postulated that removing these excipients may improve the GI tolerability of deferasirox FCT. Although the overall incidence of GI AEs was similar between the 2 treatment arms in ECLIPSE, the exposure-adjusted GI AE rate and the incidence of severe GI AEs appeared lower with deferasirox FCT than with deferasirox DT. As well as removal of the lactose and sodium lauryl sulphate excipients, the fact that deferasirox FCT may be taken with a light meal may have also contributed to this apparent improvement in the GI tolerability profile of this formulation.

Data concerning the longer-term tolerability of deferasirox FCT would be of interest, including data examining any possible effect of deferasirox FCT on renal events. Longer-term data are also needed to clarify if the improved patient adherence seen with deferasirox FCT in ECLIPSE translates into improved clinical outcomes.

### 6 | CONCLUSION

Optimising iron chelation therapy is crucial to achieve good outcomes in patients with transfusion-dependent thalassaemia or lower-risk MDS. Ensuring good adherence and preventing and managing AEs are key strategies in optimising treatment with deferasirox DT and deferasirox FCT.

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