The challenges of handling deferasirox in sickle cell disease patients older than 40 years

Lorena Bedotti Ribeiro, Eliane Alves Soares, Fernando Ferreira Costa, Simone Cristina Olenscki Gilli, Sara Teresinha Olalla Saad and Bruno Deltreggia Benites

Hematology and Transfusion Medicine Center, University of Campinas, Brazil

ABSTRACT

Objectives: Deferasirox is an oral iron chelator with established dose-dependent efficacy for the treatment of iron overload secondary to transfusion. However, there is few data reporting the use of Desferasirox in adult patients with sickle cell disease (SCD) and transfusional iron overload.

Methods: We conducted a prospective, single center, nonrandomized study from January 2014 to March 2015 in Campinas, Brazil. Seven patients (five women, median age 50 y.o.) who were followed up on regular transfusion program were treated with a single daily dose of deferasirox (median dose 20 mg/kg). They were monitored for clinical symptoms, renal function and hepatotoxicity.

Results: One patient discontinued the study due to lack of compliance. Two patients reported mild to moderate adverse events (gastrointestinal disturbances). Five patients had the drug discontinued due to severe hepatotoxicity that evolved to death; no patient finished the study.

Discussion and conclusions: Deferasirox does not appear to be well tolerated in SCD patients older than 40 years, in which complications of the underlying disease are already fully installed. The choice of the ideal iron chelator for this population should include an evaluation of comorbidities and organic dysfunctions, as well as the need to find pharmacogenetic safety markers in this group of patients.

Introduction

Patients with sickle cell disease (SCD) often require blood transfusions for the treatment of both acute and chronic complications associated with the disease. Despite the undeniable benefit of transfusion for these patients, iron overload associated with transfusion is a common complication and, if left untreated, can result in severe impairment of various organs (mainly liver, heart and endocrine glands), significantly elevating the morbidity and mortality of this disease [1,2].

The clinical experience with iron chelators in patients with transfusional hemochromatosis shows that, when performed correctly, this therapeutic modality is able to reduce the incidence of these complications, improving quality of life and overall survival [3,4]. The efficacy of chelation therapy, however, is often limited by the route of administration of the drug of choice. Deferoxamine, although efficient in the removal of body iron, should be administered subcutaneously or intravenously in prolonged infusions of 8–12 h, 5–7 days per week, which significantly decreases the adherence of patients to this regimen [5,6]. In the RELATH study (Registry of Latin Americans with Transfusional Hemosiderosis) that included 646 patients with sickle cell anemia, only a 46.3% of these patients were observed to have received chelation therapy. In this study, in which deferoxamine was the only available chelator, 20% of patients abandoned the use, primarily due to adherence issues [7].

The availability of oral Deferasirox (Exjade®) in a single dose makes this option a very attractive alternative to other iron chelators, favoring the adherence of patients to chelation therapy. The safety profile of this drug has already been demonstrated in patients with several types of transfusion-dependent anemias, especially in patients with ß-thalassemia [8–11]. In addition to the possibility of oral administration in a single daily dose, studies reporting the use of Deferasirox in patients with sickle cell disease showed a significant reduction in ferritinemia. However, in all these studies, the preferential inclusion was that of young patients, with no significant comorbidities [12–14]. After the advent of chronic therapy with Hydroxyurea and other improvements in the management of these patients, individuals with sickle cell disease currently present an expressive increase in survival, with a consequent longer exposure to transfusions and onset of comorbidities and target organ damage.
Considering the importance of adequate iron chelation therapy in patients with sickle cell disease, this study was performed to evaluate the efficacy and tolerability of using Deferasirox specifically in patients with sickle cell disease with iron overload secondary to transfusion and over 40 years of age.

Methods

This was a prospective, single center, non-randomized study conducted from January 2014 to March 2015 at the Hematology and Transfusion Medicine Center, University of Campinas, Brazil. Seven patients (2 male and 5 females) were included in the study. All patients had SCD (6 homozygous and 1 SC hemoglobinopathy). The median age was 50 (43–67) years. Patients received a median dose of 20 (12–20) mg/kg/day Deferasirox.

Patients had documented iron overload: serum ferritin > 1000 ng/ml or transferrin saturation > 50%, secondary to blood transfusion (all patients had received more than 20 units of packed red blood cells throughout life). One patient had no previous use of iron chelators, and the others had their current drug(s) switched to Deferasirox (3 of them used Deferoxamine alone, 2 used Deferoxamine associated to Deferiprone and 1 of them used Deferiprone alone).

Initial assessment included serum creatinine, creatinine clearance calculated using the Cockcroft-Gault formula and documented by Chromium EDTA, proteinuria and microalbuminuria, sodium and potassium serum levels, AST, ALT and bilirubin, serological markers for Hepatitis B and C viruses, blood counts, reticulocyte count, serum ferritin and iron concentration, total iron binding capacity (TIBC), transferrin saturation index, cardiac and hepatic magnetic resonance imaging and echocardiogram.

These tests were repeated periodically to assess the safety, efficacy, and tolerability of deferasirox. Monitoring was carried out as follows: (i) every 7 days: creatinine dosage during the first 8 weeks or until dose adjustment; (ii) every 30 days: blood counts, microalbuminuria, Na, K, AST, ALT and bilirubin; (iii) every 90 days: ferritin, serum iron, TIBC, transferrin saturation; (iv) every 180 days: MRI, echocardiogram, renal scintigraphy with Cr EDTA.

The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Institution’s Medical Ethics Committee (protocol No. 478.921). Informed written consent was obtained from all patients prior to participating in any of the study procedures. Criteria for suspension of the drug included tolerability failure and mainly progressive changes in renal or hepatic function. In the case of 2 consecutive increases of AST and/or ALT greater than 5 times the baseline values and 2 consecutive increases greater than 33% of baseline creatinine, the dose would initially be reduced by half; in the case that these changes persisted for more than 3 weeks, the medication would be discontinued [15].

The data were analyzed under the supervision of a statistics professional and were reviewed by the researchers. Safety and efficacy data are reported for all patients who received at least one dose of deferasirox throughout the study. The safety assessment was based primarily on the frequency of adverse events and laboratory values that exceeded the predetermined intervals. The main parameter of effectiveness was the alteration of the last serum ferritin performed in relation to basal ferritin. The association between variables was calculated using Wilcoxon (median difference) and Spearman non-parametric (correlation) tests. The percentage difference used in the Spearman test was calculated by subtracting the initial value from the final value of the analyzed variable divided by the initial value. P values were considered statistically significant when < 0.05.

Results

Patients’ clinical and laboratory data are depicted in Table 1. Adherence to treatment was checked at each visit by the attending physician or nurse through interviews and checking of medication withdrawal control at the pharmacy. Liver iron concentration assessed by MRI before initiation of treatment showed mean T2* of 1.8 (0.7–6.4) msec and LIC of 15.11 (3.92–39.57) mg/g.

The median serum ferritin at the beginning of treatment was 2,971 (1,453 - 13,969) ng/mL and the median transferrin saturation was 73.57 (100–22)%. The high levels of ferritin prior to treatment with Deferasirox in some of these patients are due to lack of adherence to the chelation regimen subcutaneously or intolerance to other chelators. After the initiation of Deferasirox, the median ferritin was 2,383 (284 - 12,383, p = 0.297) and the median transferrin saturation was 62.28 (44–83, p = 0.042). The correlation of the dose of Deferasirox with the percentage of reduction of

| Table 1. Patients’ clinical and laboratory data, including variation in creatinine, ALT, ferritin and transferrin saturation levels. Mean time between the two evaluations in each patient was 126 (77–269) days. |
|-----------------|-----------------|
| Clinical and laboratory data | All patients (n = 7) |
| Median age (range), years | 50 (43–67) |
| Male: Female, n | 2:5 |
| Phenotype, SS:SC | 6:1 |
| Median Dose (range), mg/kg | 20 (12–20) |
| Median baseline serum ferritin (range), ng/ml | 2971 (1453–13969) |
| Median serum ferritin after treatment (range), ng/ml | 2.383 (284–12,383), p = 0.297 |
| Median serum transferrin saturation (range), % | 73.57 (100–22) |
| Median serum transferrin saturation after treatment (range), % | 62.28 (44–83), p = 0.042 |
| Median baseline ALT (range), U/L | 35 (12–68) |
| Median peak ALT (range), U/L | 62 (17–463), p = 0.016 |
| Median baseline creatinine (range), mg/dl | 0.96 (0.69–1.24) |
| Median peak creatinine (range), mg/dl | 1.44 (1.01–1.67), p = 0.016 |
the serum ferritin in relation to the basal levels showed Ro 0.359/p = 0.43.

One patient was withdrawn from the study due to a violation of the protocol, since he did not adhere properly to the administration of the drug and failed consultation. The adverse events reported by the patients were predominantly gastrointestinal disorders (nausea, diarrhea and epigastralgia in 25% of patients) ranging from mild to moderate intensity. There was complete improvement of the symptoms after continuation of the treatment, with no need of suspending the drug, as also reported in previous studies evaluating Deferasirox [8,9].

The median baseline creatinine was 0.96 mg/dL (0.69–1.24) and the median creatinine after the introduction of Deferasirox was 1.44 mg/dL (1.01–1.67) (p = 0.016). Five patients (71.4%) had a reduction in dose followed by definitive suspension of the drug due to worsening of renal function (2 consecutive increases greater than 33% of baseline creatinine). Correlation of the dose of deferasirox with the percentage increase of the serum creatinine in relation to the basal levels showed Ro 0.677/p = 0.095. Other medications used by these patients included those routinely required in following adult patients with sickle cell disease: Hydroxyurea, folic acid, calcium with vitamin D, and angiotensin converting enzyme inhibitors. These drugs had their doses optimized before the onset of Deferasirox and there were no previous toxicities or disturbances in renal function that compromised the association with this new drug. There were no differences in microalbuminuria values in relation to the initiation of treatment [329.46 (5.03–649.98) x 355.87 (0.03–1812) mg/g, p = 0.154] and despite a decrease in estimated creatinine clearance values, they did not reach statistical significance [70.42 (45–122) x 47.78 (20–69) ml/min/1.73m², p = 0.091].

The median ALT before drug introduction was 35 U/L (12–68) and the median ALT after initiation of treatment and during the study period was 62U/L (17–463) (p = 0.016). Correlation of the dose of Deferasirox with the percentage of increase of serum ALT in relation to the basal levels showed Ro 0.418/p = 0.35.

One patient developed severe hepatotoxicity (increase of AST, ALT and bilirubin > 5 x UNL) after administration of deferasirox. This was a 43-year-old female who started 20 mg/kg/day oral DFX therapy in January 2014. She had no signs of chronic liver disease on abdominal ultrasound assessment prior to study enrolment and she initially showed a good tolerance to the medication (including normal renal and liver function). 56 days after the beginning of therapy, transaminases levels increased 4X the ULN; the drug was immediately discontinued but AST and ALT levels presented progressive elevation, and bilirubin levels were also markedly increased. A presumable diagnosis of hepatocellular drug-induced liver injury (DILI) was performed, and the injury was initially classified as moderate (score 2) according to the Drug-Induced Liver Injury Network criteria [16]. Auto-antibodies for autoimmune hepatitis (antinuclear antibody, liver and kidney microsome type 1 antibody, and smooth muscle antibody) were negative and chronic hepatitis B and C were excluded by serology and PCR. She evolved with grade III/IV encephalopathy, and a rapid clinical deterioration with refractory distributive shock and multi-organ failure, followed by cardiac arrest and death in less than 24 h. It is interesting to note that this patient had a homozygous polymorphism in the gene encoding the multidrug resistance protein (MRP2), 17774delG Abcc2 [17].

**Discussion and conclusions**

Our results demonstrate the difficulty in handling Deferasirox and its low tolerance for this group of patients who already have complications of the underlying disease. The only adverse events reported by the patients were gastrointestinal symptoms (nausea, diarrhea and dyspepsia) that were mild to moderate in intensity, transient, and did not lead to drug withdrawal. However, contrary to previous studies, in our group of patients the increase in serum creatinine was not mild and transient, resulting in the suspension of the drug in the majority of patients. Creatinine levels returned to baseline levels after discontinuation of the drug. However, subsequent re-introduction, even at smaller doses, was not possible due to further worsening of renal function.

Changes in renal function parameters were reported as an adverse event of the product in both children and adults, with increased plasma creatinine and proteinuria in 33–38% of treated patients. The effects on renal function appear to be mostly moderate, transient, and dose-dependent [12]. However, since renal toxicity can be silent and non-specific, leading to diagnosis in late stages of injury, data on the incidence and management of these events are essential for the care of these patients, especially those with SCD who may present with renal impairment due to the disease itself.

Few studies have so far evaluated the efficacy and safety of using Deferasirox specifically in patients with sickle syndromes [13–15]. Vichinsky et al. published data on 5-year cumulative safety and efficacy of deferasirox in 185 SCD transfusion-dependent patients (mean age 19.2 years, range 3–54) [14]. Increased serum creatinine levels led to dose adjustment or discontinuation in 11 (5.9%) patients. In relation to the dose used, there was no apparent difference in incidence or type of adverse events, before and after the dose increase above 30 mg/kg/day in relation to lower doses, as well as no significant differences in laboratory parameters were reported (creatinine clearance, plasma creatinine and proteinuria). In the EPIC
study, of the 1,744 patients included, 80 had sickle cell disease (mean age 23.9 years, range 4–60). The dose of Deferasirox was 20–30 mg/kg/day. Only two patients (2.5%) had consecutive serum creatinine increases of more than 33% above the baseline. The increase in serum creatinine in the study appeared to correlate with the previously increased baseline levels of the patients. There were no cases of drug-related proteinuria in patients with sickle cell disease [9]. It is important to emphasize once again that in these studies the cases consisted essentially of young patients, possibly with lesions in target organs still incipient or absent.

Regarding the patients described in our study, due to the occurrence of the previously reported hepatic and renal toxicities, the dose of the medication had to be reduced or discontinued, resulting in the administration of subdoses to many patients when compared to the doses administered in previous studies. This is probably the reason that we have not found a proven efficacy of deferasirox in reducing iron overload (accessed by ferritinemia). Therefore, this is the first study that specifically addresses the handling of Deferasirox in adult patients with sickle cell disease and transfusion iron overload. Further studies, with a larger number of patients, will be necessary to prove the initial data of this study.

The main metabolic pathway for deferasirox is glucuronidation by the subfamily UDP-glucuronosyltransferase 1A (UGT1A) which encodes UDP-glucuronosyltransferase, a glucuronidation enzyme that transforms small lipophilic molecules into excretable water-soluble metabolites. Deferasirox is then eliminated in bile through the multidrug resistance protein (MRP2) which is an organic transporter anion expressed in the canalicular membrane of hepatocytes and in the epithelium of the proximal tubule cells. MRP2 is encoded by the Abcc2 gene. Lee et al. analyzed the genetic polymorphisms of UGT1A and MRP2 to predict toxicities in a population undergoing deferasirox treatment. Their results indicated that hepatotoxicity was related to the Haplotype MRP2 and elevation of creatinine was associated with the UGT1A1 * 6 genotype [18]. Therefore, the investigation of these polymorphisms may lead to a better understanding of the pathophysiological mechanism of deferasirox-related toxicity, in order to determine the actual dosages and contraindications of the drug.

In conclusion, administration of Deferasirox at a dose of 10–20 mg/kg in patients with sickle cell disease over the age of 40 years was not well tolerated and treatment was discontinued due to changes in renal function or due to severe hepatotoxicity (that subsequently evolved to death) which were not strictly related to drug dose (Table 2).

It was not possible to prove the effectiveness of the treatment in this specific cohort of patients, since none of them reached the end of the study nor was the time of exposure to treatment sufficient to verify efficacy. We conclude that in adult patients with sickle cell anemia, the choice of the ideal iron chelator should include an evaluation of comorbidities and organic dysfunctions, as well as the need to find pharmacogenetic safety markers for the use of drugs in this group of patients.

Discussion statement
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ORCID
Sara Teresinha Olalla Saad http://orcid.org/0000-0003-0809-8068
Bruno Deltreggia Benites http://orcid.org/0000-0003-3985-5690

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Table 2. Relationship between Deferasirox dose and variation in creatinine, ALT and ferritin serum levels.

| Variable | Ro    | P value |
|----------|-------|---------|
| Creatinine | 0.677 | 0.095   |
| ALT      | 0.418 | 0.35    |
| Ferritin | 0.359 | 0.43    |
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