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CLINICAL CASE

Deferasirox and Complex Proximal Tubulopathy. Presentation of two clinical cases

Deferasirox y Tubulopatía Proximal Compleja. Presentación de dos casos clínicos

Carmen Niño Taravilla[a,b,c], Áurea Cervera Bravo[d], Hugo Otaola Arca[e], Julián Sevilla[f], Cristina Aparicio López[g]

[a]Servicio de Cuidados Intensivos Pediátricos. Hospital Infantil Universitario Niño Jesús. Madrid, España
[b]Unidad de Paciente Crítico Pediátrico. Hospital Roberto del Río. Santiago, Chile
[c]Unidad de Paciente Crítico Pediátrico. Clínica Indisa. Santiago, Chile
[d]Servicio de Nefrología Pediátrica. Hospital Universitario de Móstoles. Madrid, España
[e]Servicio de Urología, Clínica Alemana. Santiago, Chile
[f]Servicio de Hemato-Oncología Pediátrica, Hospital Infantil Universitario Niño Jesús. Madrid, España
[g]Servicio de Nefrología Pediátrica, Hospital Infantil Universitario Niño Jesús. Madrid, España

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What do we know about the subject matter of this study?

Treatment with iron chelators, such as Deferasirox, is essential to avoid the iron overload that can occur in patients requiring periodic transfusions. However, side effects, such as renal involvement, both glomerular and tubular, are not exempt.

What does this study contribute to what is already known?

Renal damage secondary to the use of Deferasirox is dose-dependent and occurs more frequently in patients who present dehydration. If it occurs, an early reduction of the dose or even its suspension should be considered.

Abstract

Treatment with iron chelators is essential for patients with iron overload secondary to repeated transfusions. Deferasirox is the first once-daily oral active iron chelator. As a result, therapeutic adherence has improved, reducing the complications of iron overload, especially heart failure. However, it is not exempt from possible side effects, such as kidney involvement, which is more frequent in children. **Objective:** To report 2 patients with Diamond-Blackfan anemia (DBA) who developed impaired renal function secondary to the administration of Deferasirox. **Clinical Cases:** *Case 1.* A 15-year-old adolescent diagnosed with DBA undergoing treatment with periodic transfusions and Deferasirox. During an acute gastroenteritis, she developed acute renal failure along with complex proximal tubulopathy. *Case 2.* A 5-year-old boy diagnosed with DBA receiving periodic transfusions and treatment with Deferasirox. He presented polyuria with laboratory abnormalities compatible with acute renal

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Correspondence:
Carmen Niño Taravilla
carmen.nino@hotmail.com

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failure and proximal tubular dysfunction. In both cases, they were adequately hydrated and Deferasirox was temporarily suspended, improving renal function. **Conclusion:** Based on these cases, close monitoring of renal and tubular function, as well as ferritin levels, is recommended in patients receiving Deferasirox. In the presence of intercurrent processes, adequate hydration should be performed, and an early dose reduction or drug administration interruption should be considered in cases of kidney involvement.

Introduction

Iron overload due to multiple red blood cell transfusions is a major problem in patients with thalassemia major, sickle cell disease, myelodysplastic syndrome, and other uncommon anemias. Blood transfusions result in iron overload that accumulates in the liver, endocrine tissues, and myocardium. Before the development of iron chelators, patients with these diseases died during childhood or early adulthood, mainly due to the development of heart failure[1].

Deferoxamine is an iron-chelating agent available since the 1960s, which has helped in the management of these patients. However, it has a very short half-life and poor bioavailability and must be administered subcutaneously or intravenously, limiting its effectiveness due to poor therapeutic adherence[2].

Deferasirox is the first orally active iron chelator with a single daily administration. It binds iron with high affinity, promoting its excretion in the feces. It is indicated in the treatment of chronic iron overload due to blood transfusions (> 7 mL/kg/month of red cell concentrate) or when treatment with Deferoxamine is contraindicated[3,4]. The initial dose is 20 mg/kg, adjusted every three to six months, for a ferritin target level between 500 to 1000 ng/mL.

The most frequent adverse effects are gastrointestinal (nausea, vomiting, diarrhea, or abdominal pain), cutaneous (exanthema), nephrological (high creatinine levels and proteinuria), and hepatobiliary (increased transaminases). Among the infrequent adverse effects are high-frequency hearing loss, lens opacities, and tubulopathy, with the latter occurring more frequently in children and adolescents[3]. The objective of this work is to present 2 patients with Diamond-Blackfan anemia (DBA) with renal function impairment secondary to the administration of Deferasirox, as well as a review of the literature.

Clinical Cases

Clinical Case 1

15-year-old adolescent diagnosed with DBA at 3 months of life, with no personal or family history of renal disease. She was treated with corticosteroids from 3 months to 6 years of age. Subsequently, she presented resistance to prednisone, so treatment was started with periodic transfusions every 3 weeks (20 ml/kg/month). Laboratory tests showed iron overload (ferritin > 1000 ng/mL) and MRI images compatible with hepatic iron overload, so treatment with Deferoxamine was started. She developed cutaneous abscesses in the puncture sites, so the iron chelator was changed to Deferasirox (23 mg/Kg/day).

During acute gastroenteritis, she presented acute renal injury (AKI), with a moderate increase in creatinine, but with a BUN-to-creatinine ratio below 20 (Table 1), in addition to hypokalemia, hypophosphatemia, and hypouricemia (Table 1). A renal ultrasound was performed, which showed normal images, and a complete renal panel showed non-nephrotic range proteinuria (protein-to-creatinine ratio 0.47 mg/mg creatinine) of tubular nature with beta-2 microglobulin of 23.8 mg/L (normal values 0-0.2 mg/L), all signs compatible with complex proximal tubulopathy.

The patient was not receiving any other drug causing tubulopathy, therefore, treatment with the iron chelator was suspended, starting treatment with oral potassium and phosphate supplements, showing normal values in the analysis 24 days after suspension of the chelator (Table 1). After this, the potassium and phosphorus supplements were decreased, and after 4 months, treatment was restarted with Deferasirox at a lower dose (16 mg/kg/day), with exhaustive monitoring of renal function and ferritin levels, both of which remained within adequate ranges.

Clinical Case 2

A 5-year-old boy diagnosed with DBA at 2 months of age. He received periodic transfusions (18 ml/kg/month) from the beginning since at diagnosis he did not respond to corticosteroid treatment. At 2 years of life, he started treatment with Deferasirox (10 mg/kg/day), but the dose was progressively increased up to 30 mg/kg/day due to the detection of hepatic iron overload by MRI, with ferritin levels of 500 ng/mL, adequate for the treatment objective with the chelator.

He visited the emergency department due to poor general condition, abdominal pain, polyuria, and

vomiting, showing signs of moderate dehydration on the physical examination. Complementary tests showed prerenal AKI (BUN-to-creatinine ratio 42), stage 1 according to the KDIGO 2012 criteria. Metabolic acidosis, hypokalemia, hypophosphatemia, hypouricemia, and glycosuria were also observed (Table 1), which were compatible with proximal tubule dysfunction.

Treatment with Deferasirox was suspended and restarted at lower doses (5 mg/kg/day) after correction of the analytical alterations (Table 1), with renal function and ferritin monitoring. The dehydration was caused by polyuria and vomiting, secondary to tubulopathy resulting from a higher dose of chelator than was necessary at the time for iron overload since his ferritin level was 200 ng/mL.

Discussion

DBA is characterized by selective congenital pure red cell hypoplasia, defined by macrocytosis, reticulocytopenia, and marked decrease or absence of the erythroid compartment in bone marrow, without involving the rest of the hematological series. Its incidence is 5 cases per 1,000,000 live births per year[5]. Both sexes are equally affected, and no ethnic predisposition has been identified. It presents autosomal dominant inheritance with variable penetrance. Currently, disease-causing mutations have been identified in 40-45% of patients, all of them related to genes coding for ribosomal proteins.

Half of the patients with DBA have short stature and other congenital anomalies, and the most frequent is the craniofacial one (Pierre-Robin sequence and cleft palate), followed by urogenital and thumb anomalies. Diagnosis is usually made in the first 2 years of life in children with anemia, erythroblastopenia, family history (10-20% of cases), associated malformations (40% of cases), and high adenosine deaminase (ADA) levels in erythrocytes, which is a frequent but not specific sign of DBA. The differential diagnosis should

Table 1. Laboratory data in 2 patients with Blackfan Diamond anemia.

	Case 1		Case 2	
	Fanconi syndrome	24 days after suspension of Deferasirox	Fanconi syndrome	13 days after suspension of Deferasirox
Creatinine (mg/dL) (NV: 0.3-1)	0.68	0.43	0.6	0.3
Urea (mg/dL) (NV: 10-50)	28	21	55	34
Ureic nitrogen (mg/dL) (NV: 6-20)	13	9.8	25.6	15
Sodium (mEq/L) (NV: 135-145)	137	140	132	140
Potassium (mEq/L) (NV: 3.5-5.5)	2.6	3.5	2.9	4
Phosphorus (mg/dL) (NV: 3-5)	1.6	4	1.7	4.7
Uric acid (mg/dL) (NV: 2.5-6)	1.2	2.5	0.8	0.9
Calcium (mg/dL) (NV: 9-10.5)	8.87	9.16	8.6	9.3
pH (NV: 7.35-7.45)	7.33	7.36	7.17	7.36
Bicarbonate (mmol/L) (NV: 22-30)	21.6	24.9	10.8	21
Ferritin (ng/mL) (NV: 30-250)	203	248	200	395
Osmolarity (mmol/Kg) (NV: 270-300)	287	283	263	282
FE Sodium (NV: < 1%)	1.33	0.38	0.4	0.45
FE Potassium (NV: < 14%)	20.57	6.61	18.5	5.1
FE uric acid (NV: < 12%)	44.92	15.03	62	25.4
TPR (NV: > 80%)	65	82	65	88
Calcium/Cr (mg/mg) (NV: < 0.2)	0.55	0.13	1.1	0.39
Glucosuria	Negative	Negative	Positive	Negative
Microalbuminuria (mg/g Cr) (NV < 20)	46.39	6.02	200	19
Beta-2 microglobulin (mg/L) (NV: 0-0.2)	23.8	< 0.21	ND	1.57
Urinary osmolarity (mmol/Kg) (NV: 300-1000)	220	632	490	733

NV: normal value. FE: fractional excretion. TPR: Tubular phosphate reabsorption. NA: Not available. Cr: creatinine.

include transient erythroblastopenia, parvovirus B19 infection, and other congenital anemias.

Corticosteroids are the treatment of choice, achieving remission in 50-70% of cases. Corticosteroid resistance occurs in 35% of DBA cases. These patients should receive therapy with periodic red blood cell transfusions and may be candidates for hematopoietic stem cell transplantation. Disease severity is variable, but they are at increased risk for diseases such as myelodysplastic syndrome and certain cancers[6].

Treatment with iron chelators is essential for patients with iron overload secondary to repeated transfusions, due to different types of anemia, such as DBA. Currently, Deferasirox is the first-choice iron chelator because its dosage has improved the therapeutic adherence of these patients, as well as improving the complications derived from iron overload, especially heart failure.

Since Deferasirox was first marketed in 2005, isolated cases of secondary renal involvement have been described[7], both at the glomerular and tubular level, in adults and children. In the latter, it is especially important to check for renal involvement, since, according to the datasheet, the possibility of renal tubulopathy is greater in children and adolescents.

The pathophysiological mechanisms that cause tubular toxicity are unknown. Some theories suggest that it could be due to increased iron absorption by tubular cells. Other authors have observed in primates a 40% reduction in the iron concentration levels of the kidney, causing secondary alterations in tubular function[8,9].

Regarding glomerular involvement, an increase in baseline creatinine has been observed secondary to the use of Deferasirox[10], especially during the first 6 months of administration[11]. An association has also been described between the rapid decrease in ferritin levels and the appearance of renal toxicity[12], which could be related to higher-than-necessary doses, resulting in over-chelation[3]. This fact has also been described by Bird et al[13], who reported a case series of 1213 children between 2 and 15 years of age treated with Deferasirox, finding 162 cases of AKI. They observed a 1.26-fold relative risk (RR) (95% confidence interval (CI): 1.08-1.48, p = 0.004) of developing AKI for each 5 mg/kg/day increase over the typical initial dose of 20 mg/kg/day of Deferasirox. They also demonstrated that high doses of Deferasirox (> 30 mg/Kg/day) increased the risk for AKI (RR = 4.47, 95% CI: 1.25-15.95, p = 0.02) when serum ferritin was lower than 1000 ng/mL, especially in children aged between 2 and 6 years. With these results, they concluded that Deferasirox causes AKI depending on the dose, especially if there are concomitant low ferritin values, with overchelation as the triggering factor for renal damage.

There are other smaller case series in the literature. Dubourg et al[14] described a series of 10 pediatric patients with thalassemia major who presented renal damage secondary to the use of Deferasirox. In 8 of the patients, they observed decreased glomerular filtration rate, and 2 presented complex proximal tubulopathy or Fanconi syndrome (FS). Dee et al[9] reported a series of 18 patients with thalassemia major who were on treatment with different iron chelators, 9 of them received Deferasirox. 12 patients presented FS, 9 of them were treated with Deferasirox. As in our cases, in both studies, all patients normalized renal function after discontinuation or reduction of the dose.

Based on the above, we recommend performing weekly monitoring of renal function (measure serum creatinine and creatinine clearance Schwartz estimate and/or plasma cystatin C levels along with plasma and urine electrolytes) during the first month of treatment or after a dose modification. If it remains normal, controls could be performed monthly thereafter[3]. As previously noted, ferritin levels should be monitored every 3-6 months for dose adjustment, with a target value of 500-1000 ng/mL.

We present two clinical cases with glomerular and tubular renal involvement secondary to the use of Deferasirox. The tubular involvement was the FS characterized by variable renal loss of phosphorus, bicarbonate, sodium, potassium, chloride, uric acid, amino acids, glucose, and low molecular weight proteins. FS can be primary or secondary to other diseases (fructosemia, galactosemia, tyrosinemia, among others), drugs (antibiotics, cytostatics), toxics (heavy metals), or immune diseases. In our cases, it was associated with the use of Deferasirox. Glomerular involvement occurred in both cases during acute dehydration, who were receiving a higher dose of chelator than necessary since both patients had adequate ferritin levels at the time of consultation (200 and 203 ng/mL, respectively). Both patients normalized renal and tubular function after drug discontinuation. During follow-up, the chelator dose was reduced, and renal function and ferritin values were closely monitored, with no new episodes of AKI or tubular involvement in either child.

Conclusion

Monitoring of renal function and adjustment of chelator dose according to ferritin levels is essential in patients receiving treatment with Deferasirox. In addition, in the presence of intercurrent processes, the patient should maintain adequate hydration, due to the risk of AKI. If renal or tubular toxicity develops, early dose reduction or discontinuation of the drug should be considered to avoid progression of renal injury.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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References

1. Hershko C. Iron loading and its clinical implications. Am J Hematol. 2007;82:1147-8.
2. Lindsey WT, Olin BR. Deferasirox for transfusion-related iron overload: a clinical review. Clin Ther. 2007;29(10):2154-66.
3. Ficha técnica de Exjade®. Novartis Europharm Limited. [Internet]. [cited 2020 Oct 14]. Available from: https://ec.europa.eu/health/documents/community-register/2017/20170814138420/anx_138420_es.pdf
4. European Medicines Agency. Exjade®. Europena Public Assesment Reports (EPAR). [Internet]. European Medicines Agency 2018 [cited 2020 Oct 14]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/exjade
5. Bravo LM, Rodríguez ZN. Anemia de Diamond-Blackfan: Experiencia clínica en 20 pacientes (1968-1998). Rev Chil Pediatría 2000 ;71(3): 192-6.
6. Da Costa L, Leblanc T, Mohandas N. Diamond-Blackfan anemia. Blood. 2020;136(11):1262-73.
7. Bhandari S, Daar S. Deferasirox and renal dysfunction in children. Pediatr Nephrol. 2012;27(11):2159.
8. Yacobovich J, Stark P, Barzilai-Birenbaum S, et al. Acquired proximal renal tubular dysfunction in β-thalassemia patients treated with deferasirox. J Pediatr Hematol Oncol. 2010;32(7):564-7.
9. Dee CMA, Cheuk DKL, Ha S-Y, Chiang AK-S, Chan GC-F. Incidence of deferasirox-associated renal tubular dysfunction in children and young adults with beta-thalassaemia. Br J Haematol. 2014;167(3):434-6.
10. Grangé S, Bertrand DM, Guerrot D, Eas F, Godin M. Acute renal failure and Fanconi syndrome due to deferasirox. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2010;25(7):2376-8.
11. Cappellini MD, Bejaoui M, Agaoglu L, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood. 2011;118(4):884-93.
12. Rheault MN, Bechtel H, Neglia JP, Kashtan CE. Reversible Fanconi syndrome in a pediatric patient on deferasirox. Pediatr Blood Cancer. 2011;56(4):674-6.
13. Bird ST, Swain RS, Tian F, et al. Effects of deferasirox dose and decreasing serum ferritin concentrations on kidney function in paediatric patients: an analysis of clinical laboratory data from pooled clinical studies. Lancet Child Adolesc Health. 2019;3(1):15-22.
14. Dubourg L, Laurain C, Ranchin B, et al. Deferasirox-induced renal impairment in children: an increasing concern for pediatricians. Pediatr Nephrol. 2012;27(11):2115-22.