Significant Hyperbilirubinemia and Acute Hepatocellular Jaundice in a Pediatric Patient Receiving Deferasirox: A Case Report

Elizabeth A. Feldman, PharmD; Christopher D. Miller, PharmD; Sarabeth Wojnowicz, PharmD; and Robert Seabury, PharmD

Despite a boxed warning, postmarketing reports of deferasirox-associated hepatic injury in patients with chronic transfusions are not well described. Hepatic impairment, including failure, has been reported to occur more frequently in patients older than 55 years and in those with significant comorbidities, including liver cirrhosis and multiorgan failure. In this case report, we describe significant hyperbilirubinemia and acute hepatocellular jaundice related to deferasirox in a 7-year-old female being treated for iron overload secondary to chronic transfusions. This report outlines a unique case without preexisting risk factors in which other causes of liver injury are excluded as defined by the Roussel Uclaf Causality Assessment Method, which indicates a probable score of deferasirox causing the injury.

ABBREVIATIONS ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method

KEYWORDS adverse drug effect; deferasirox; drug hepatotoxicity; drug-induced liver injury; hepatocellular; hepatotoxicity; jaundice; RUCAM

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Introduction

The accumulation of iron secondary to chronic red blood cell transfusions is a known complication in patients with various anemias.¹ Ineffective erythropoiesis secondary to increased intestinal iron absorption leading to iron overload can lead to increased morbidity and mortality without treatment. Deferasirox, an oral iron chelator, is an effective agent to reduce total body iron in patients with transfusion iron overload, and chronic iron overload in patients with non-transfusion-dependent thalassemias.² The agent is generally well tolerated, with the most frequent reported adverse reactions being diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine.³ Warnings regarding hepatic toxicity, including hepatic failure, have more recently been reported and are now included on the labeling of deferasirox. Previous reports^{4–7} describing liver injury secondary to deferasirox often could not solely be attributed to deferasirox alone and seldom were associated with significant hyperbilirubinemia. The purpose of this case report is to describe drug-induced hepatocellular liver injury with significant hyperbilirubinemia secondary to deferasirox in a pediatric patient with no other known or identifiable cause of acute hepatic injury.

Case Presentation

A 7-year-old, 19.6-kg female with a past medical history of pyruvate kinase deficiency and severe chronic

anemia requiring chronic transfusions, presented with diffuse jaundice and lethargy. She had no personal or family history of hemochromatosis. The patient experienced iron overload secondary to chronic transfusions and had been prescribed oral iron chelation therapy with deferasirox (Jadenu, Novartis, Basel, Switzerland) 270 mg (13.8 mg/kg) daily. The patient had a history of non-compliance with her deferasirox therapy which, according to her parents as assessed by chart note documentation, had recently improved prior to admission. Her other home medications include oral folic acid 2 mg/day and a daily pediatric multivitamin. Her family history is positive for mildly low pyruvate kinase levels (father), and her social history is unremarkable. Most recent laboratory results prior to admission (and consistent with previous baseline results) were as follows: alanine aminotransferase (ALT), 29 units/L; aspartate aminotransferase (AST), 79 units/L; alkaline phosphatase, 204 units/L; and total bilirubin, 2.5 mg/dL.

Her father stated she had a 2-month history of intermittent abdominal pain that had not been associated with any jaundice. The intermittent abdominal pain had initially been attributed to deferasirox. According to the parents the pain improved after the 270-mg dose was divided into twice-daily dosing. Her last transfusion was 31 days prior to admission. One day prior to admission the parents noted that the child was pale and had 1 episode of non-bilious emesis. The next morning, she awoke with diffuse jaundice, including scleral icterus. Upon presentation to her pediatrician, she was found

Table. RUCAM Scoring Breakdown for Hepatocellular Injury

RUCAM Criteria	Patient's Score	Justification
Time to onset	+1	Patient was receiving medication for the first time, with time of onset >90 days.
Course	+3	ALT fell by >50% from the peak value within 8 days following discontinuation of deferasirox.
Risk factors	+0	Patient's age is ≤55 y and her social history is negative for alcohol use.
Concomitant drug(s)	+0	No other known hepatotoxic medications were taken preceding the liver injury.
Search for non-drug causes	+2	All causes in groups I* and II* were reasonably ruled out.
Previous information on hepatotoxicity of the drug	+2	Deferasirox is stated to be a potential cause of drug-induced liver disease in the product label.
Response to readministration	+0	The drug was not readministered.
Total score	+8	

RUCAM, Roussel Uclaf Causality Assessment Method

*Group I ruling-out criteria included: viral hepatitis A, B, and C; biliary obstruction; alcoholic liver disease; and ischemic hepatitis.

*Group II criteria included complications of underlying diseases or conditions.

to have a total bilirubin concentration greater than 20 mg/dL. Subsequently, the patient was transferred to our institution for further management and workup.

Upon admission, the patient's liver enzymes were elevated: AST, ALT, and alkaline phosphatase were 983 units/L, 773 units/L, and 267 units/L, respectively. Total bilirubin and direct bilirubin were also elevated, at 36.6 mg/dL and 33 mg/dL, respectively. Additionally, serum ferritin was 8150 ng/mL (reference range, 13–150 ng/mL), iron was 204 mcg/dL (reference range, 50–120 mcg/dL), and iron saturation was 63.9% (reference range, 20%–55%). The patient was afebrile, with a normal white blood cell count and normal renal function. Physical exam showed diffuse jaundice and bilateral sclera icterus. Viral panels for Epstein-Barr virus, cytomegalovirus, and hepatitis A, B, and C were negative. Dubin-Johnson syndrome was ruled out by urine porphyrins. Deferasirox was held because of the acute hepatic toxicity, and the patient was started on ursodiol 200 mg orally twice daily.

On day 2 of admission, magnetic retrograde cholangiopancreatogram impressions showed no evidence of intrahepatic or extrahepatic biliary ductal dilation, with findings consistent with secondary hemochromatosis and renal siderosis. The patient's average liver iron concentration was determined to be 15.3 mg/g dry tissue (reference range, 0.17–1.8 mg/g). AST, ALT, and alkaline phosphatase had trended down to 556 units/L, 588 units/L, and 262 units/L, respectively. Total and direct bilirubin had also decreased to 35.1 mg/dL and 31.2 mg/dL, respectively. The patient's jaundice was also noted to have improved.

During days 3 through 5 of admission, the patient's laboratory studies assessing hepatic function continued to trend down. Non-drug causes that had been ruled out as causes included biliary obstruction, Epstein-Barr vi-

rus, cytomegalovirus, Dubin-Johnson syndrome, acute hepatitis A, B, and C, and others (Table). The patient was discharged on day 5 of hospitalization. Although still unclear, the ultimate etiology of the toxicity was thought to be caused by an acute-on-chronic insult to the liver and biliary tree and was attributed to a combination of transfusional iron overload, deferasirox toxicity, and infection.

Five days after discharge, both direct and total bilirubin continued to trend down to 7 mg/dL and 3.4 mg/dL, respectively. Direct bilirubin was 1.9 mg/dL at a follow-up appointment 10 days after discharge.

Discussion

Deferasirox, an orally active selective chelator of iron (Fe^{3+}), has an indication for the treatment of chronic iron overload due to blood transfusions in patients 2 years and older.³ This indication received accelerated approval based on a reduction of liver iron concentrations and serum ferritin concentrations. Controlled clinical trials of deferasirox in patients with myelodysplastic syndrome and chronic iron overload due to blood transfusions have not been performed. Deferasirox is available in 2 preparations: Exjade and Jadenu. Because of increased bioavailability, the dosing for the Jadenu product is approximately 30% lower than Exjade. The recommended starting dosage of Jadenu for the indication of transfusion-dependent iron overload is 14 mg/kg/day.

Premarketing studies³ reported hepatic toxicity in 1.3% ($n = 4$) of patients receiving deferasirox for beta-thalassemia for a duration of 48 weeks. All cases, including drug-induced hepatitis and increased serum transaminases, resulted in discontinuation of the drug. The manufacturer described the cases of hepatic toxic-

ity to be more common in patients older than 55 years and the cases of hepatic failure to be more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure. Limited current literature⁸ describes deferferasirox-induced liver injury in patients with underlying liver disease, likely because of these warnings.

Manufacturing data available regarding the safety and efficacy of deferferasirox for transfusional iron overload, as described in clinical studies, describe findings to those for adults for 292 pediatric patients ages 2 to younger than 16 years. Reports of hepatobiliary disorders, including hepatic failure, have been spontaneously reported during postapproval use of deferferasirox in the transfusional iron overload setting. Current literature⁴⁻⁷ describes several case reports of liver failure in pediatric patients that is attributed to deferferasirox treatment. The onset of acute liver injury ranged from 3 months to years in these pediatric case reports.

Explanations regarding the mechanism of deferferasirox-associated hepatic toxicity are poorly elucidated. Deferferasirox is metabolized largely by glucuronidation and biliary excretion.³ As described in several studies,^{9,10} deferferasirox treatment resulting in a decrease in serum ferritin concentration was associated with a corresponding decrease in ALT. In more uncommon, but severe and potentially fatal instances, the pattern of injury was typically hepatocellular, with marked elevations in serum aminotransferase. The use of pharmacogenetic biomarkers to identify functional genetic variants of enzymes that metabolize and transport deferferasirox has also been investigated^{11,12}; however, no link has been established. Ultimately, the mechanism accounting for serum enzyme elevations during deferferasirox therapy remains unknown.

The case presented describes a probable hepatic injury from deferferasirox as defined by the Roussel Uclaf Causality Assessment Method (RUCAM) score, a scoring tool used to assess the likelihood of drug-induced liver injury (DILI). A calculated R-ratio of 34 aided in the classification of hepatocellular injury. The RUCAM score of +8 is depicted in the Table and indicates deferferasirox as the probable cause of injury in our case. The onset of injury, although greater than 90 days from the initiation of deferferasirox, is similar to other case reports described in pediatric patients.^{4,5,7} This report adds to the current medical literature because it provides a unique case in which other causes of liver injury were able to be excluded.

Ling et al⁴ describe a case with a congenital disorder that increased the patient's risk for hepatotoxicity. Ramaswami et al⁵ described a case without significant hyperbilirubinemia and jaundice in a patient with an elevated white blood cell count and a panel that was positive for respiratory syncytial virus. Menaker et al⁶ describe an idiosyncratic case of acute hepatic failure after long-term deferferasirox therapy in a patient who

Figure 1. Dynamic changes in serum liver enzymes over time.

also had concomitant acute kidney injury, coagulopathy, encephalopathy, and, most notably, a ferritin concentration of 218 ng/mL (<500 ng/mL), thereby inherently increasing the risk for toxicity in the setting of increased free-drug exposure. Vichinsky et al⁷ describes elevations in ALT greater than 5 times the upper limit of normal in 3.8% of patients ages 3 to 54 years who were receiving deferferasirox; however, this finding was in the absence of changes in alkaline phosphatase or bilirubin concentrations.

Following discontinuation of deferferasirox in this case, the patient's serum liver enzymes and bilirubin improved, as depicted in Figures 1 and 2, respectively. In addition, the patient was not on any other concomitant drugs that could have caused liver injury and had no other notable risk factors for liver injury, with the exception of iron overload.

Chronic iron overload has previously been associated with end-organ damage, including hepatic dysfunction.¹ Generally, these disorders are insidious in nature, and the rapidity of symptom onset in our patient would suggest the potential for an alternative explanatory process. Our patient's symptoms started shortly after improved compliance with deferferasirox and resolved within days of medication discontinuation. Although iron overload could be a potential contributory factor, the time course of our patient's clinical picture would more likely indicate an acute disorder. In the absence of overdose and an appropriately prescribed dose, the patient's hyperchromatosis upon admission makes it unlikely that clinically relevant free-drug exposure would account for the injury.

Limitations of this case report include the inability to assess the patient's response to readministration of the drug, which is arguably the most definitive mean

Figure 2. Dynamic changes in serum bilirubin concentrations over time.

● Bilirubin, total; ■ Bilirubin, direct

* Day 0 indicates baseline values prior to initiation of deferasirox.

of DILI diagnosis, and the limitations that are inherent in using the RUCAM score to assess liver injury.¹³ Using a standardized causality assessment scale, such as the RUCAM score,¹⁴ does enhance the objectivity of the case assessment but does not substitute clinical judgment and uses criteria that may be restrictive and arbitrarily weighted, leading to incorrect evaluations. Although the RUCAM score is not a definitive tool, it does suggest probable DILI secondary to deferasirox. Moreover, this does represent an isolated case of DILI in which other sources and causes of injury were excluded or deemed to be unlikely both clinically and via laboratory testing.

Conclusion

Case reports describing a clear association between hepatic injury and deferasirox, with other potential causes ruled out, are extremely limited. Given the isolated nature of the case described in relation to other probable causes being ruled out, deferasirox was likely the causative agent of DILI. Although the mechanism regarding DILI due to deferasirox is unknown, this case emphasizes the importance of taking DILI into consideration with medications known to be hepatotoxic. Further research, including pharmacogenomics, is needed to establish the mechanism by which deferasirox causes liver injury in the absence of other causes.

ARTICLE INFORMATION

Affiliations Department of Pharmacy, Upstate University Hospital, Syracuse, New York

Correspondence Elizabeth A. Feldman, PharmD; feldmane@upstate.edu

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