INTRODUCTION
Drug induced liver injury (DILI) is a common and significant clinical problem caused by a large number of medicines by a variety of known and unknown mechanisms with variable outcomes. Deferasirox was approved by the FDA in 2005 as an iron chelator to treat chronic iron overload in patients requiring multiple blood transfusions.1 Though phlebotomy is the treatment of choice for hereditary hemochromatosis (HH), iron chelators are frequently being used for patients intolerant of or contraindicated for phlebotomy. There have been few post-market reports of hepatic injury in patients taking this medicine but the mechanism of liver injury is unknown.

We are describing a case report of acute liver injury secondary to Deferasirox in a patient with underlying liver disease and will discuss possible mechanisms of hepatotoxicity with this medicine.

CASE REPORT
A 63-year-old Caucasian female recently diagnosed with hereditary hemochromatosis (HH) presented to the emergency room complaining of a one-month history of nausea, crampy abdominal pain, fatigue, dark urine, and yellowish discoloration of both skin and eyes. Review of other symptoms included progressive fatigue and 6-8 watery bowel movements every day, both beginning approximately one month ago. The patient denied any episodes of confusion, abnormal bleeding, or any other symptoms.

Further questioning revealed that she had recently lost a family member to end-stage liver disease secondary to HH, prompting laboratory screening. Upon discovering an abnormally high ferritin level, > 1500 ng/ml, she underwent genetic testing which confirmed her diagnoses of HH. The patient refused liver biopsy and did not tolerate phlebotomy at that time because of a fear of needles. Subsequently, she was started on Deferasirox (500 mg, three times a day) for the treatment of iron overload. After one month of treatment, she came symptomatic for above. Continuing the medication, her symptoms increased in frequency and severity for several weeks, and one week prior to presentation, she noticed increasing fatigue and jaundice.

Her past medical history, aside from HH, was significant for hypertension. Her medications included lisinopril, low-dose estrogen and Deferasirox. She reported allergy to codeine and denied any prior alcohol or tobacco use. Her family history included several nieces and nephews with hereditary hemochromatosis, as well as hypertension.

Physical examination at the time of presentation revealed a pulse 86 beats/minute, blood pressure of 97/57 mmHg, and temperature of 98.6°F. The patient was oriented to time, place and person. Pertinent findings on examination included sclera icterus, mild jaundice, and mild right upper quadrant tenderness without rebound or guarding. There was no evidence of ascites on examination. No peripheral edema was noted in her extremities. Cardiovascular, respiratory, and neurological examinations were unremarkable.

Laboratory examination on admission revealed a WBC of 15.4 K/cmm, haemoglobin of 10.2 g/dl, and platelet count of 216 K/cmm. Total bilirubin of 13.2 mg/dl (direct bilirubin 7.1 mg/dl) and alkaline phosphatase 395 IU/L were both elevated from previous values of 0.8 mg/dl and alkaline phosphatase of 101 IU/L, respectively. AST of 105 units/L and ALT of 115 units/L were increased from previous recordings of 93 and 91 prior to treatment with Deferasirox. BUN and creatinine were determined to be 52 mg/dl and 3.2 mg/dl (baseline 0.9 mg/dl). Her INR was 1.1.

She was admitted to a local hospital with the diagnosis of acute hepatitis and acute renal failure. All medications were immediately stopped. She started having transient episodes of confusion. At that time, she was transferred to our facility for consideration for liver transplant.
During her hospital course, the patient was started on enteral feeding and given intravenous fluids. Along with supportive care and close monitoring, she underwent a complete workup of acute liver injury to exclude viral, serological, and autoimmune etiologies, all of which were negative. The patient's ultrasound displayed normal gallbladder with minimal ascites.

Over next few days, she not only demonstrated steady improvement of her mental status but also her hepatic and renal functions improved, obviating the need for a transplant. The patient was discharged from hospital after 2 weeks with her renal and hepatic function returning towards baseline. A liver biopsy prior to discharge revealed focal macrovesicular steatosis, mild portal inflammation (mild portal non-specific chronic active inflammation), and increased fibrous tissue. Trichrome staining highlighted increased fibrous tissue and bridging fibrosis, while iron staining showed extensive iron pigments, consistent with the diagnosis of HH.

The patient was followed-up for 6 months after discharge without any adverse outcomes. She later on decided to have phlebotomy treatments with the aid of anti-anxiety medications.

**DISCUSSION**

Medicines that cause predictable dose-related toxicity, such as acetaminophen, have generally well understood mechanisms. However, a significant number of reactions are idiosyncratic and poorly understood, accounting for 13-17% of episodes of acute liver failure.2

As previously mentioned, iron chelators are increasingly being used to treat HH patients with contraindications (anemia, cirrhosis) or aversions to phlebotomy therapy. Most of the literature refer to using Deferoxamine, an older, well-studied iron chelator. Deferoxamine therapy, however, is quite cumbersome, requiring parenteral administration several times a day.3 The introduction of Deferasirox, an orally administered iron chelator, appears to be a more convenient alternative.4 Pre-marketing studies demonstrated isolated elevations liver transaminases in almost 1/3 of patients. While these initial reports documented only non-sustained elevations, in September 2007, the FDA updated postmarket safety findings of this agent, previously documenting incidents of renal failure to include adverse hepatic events, including drug-induced hepatitis and liver failure.5,6

There have been few postmarketing notifications of hepatic failure some with fatal outcome to FDA. Most of these events occurred in patients greater than 55 years of age with significant comorbidities including liver cirrhosis and multiorgan failure.

A general analysis of drug-induced liver injury should include a careful examination of the patient's presentation and history. The above patient presented with hepatocellular jaundice, which provides valuable insight into the severity of the reaction. Hy's law based on the observations of Hyman Zimmerman, suggests the development of jaundice in the setting of drug-induced hepatocellular injury portends a more severe hepatic injury as seen in the presented case.7 The rationale behind this finding is that while transaminases signal only the presence of hepatic injury, the increasing bilirubin provides an indication of the severity of that injury, since the injury must be substantial enough to impair hepatic function. Timing of drug administration and liver injury help in finding the cause of liver injury. Women generally predominate among patients with DILI. Coexistent liver disease is another important consideration in cases of DILI, and must be ruled out as the cause for liver dysfunction before the injury can be attributed to the drug.8 Further, it appears that in many instances, any pre- or co-existent disease impacts the patients' recovery, based on hepatic reserves, and not their susceptibility to idiosyncratic DILI. Though the patient had elevated transaminases at the time of diagnosis, it is difficult to determine the extent of prior liver damage as the patient deferred a liver biopsy at that time.

Though it has been proposed that in some instances, susceptibility to DILI is independent of liver dysfunction, postmarket surveillance, as well as the presented case, suggest Deferasirox-induced hepatic failure or injury is seen particularly in patients with prior liver disease. This finding argues against idiosyncrasy, an unpredictable and dose-independent drug reaction.

The underlying mechanisms of idiosyncratic reactions are poorly understood, but it is thought to be related to genetic differences in CYP-450 expression.8,9 Several mechanisms have been proposed for DILI including production of reactive intermediates by cytochrome P450, stimulation of autoimmunity, apoptosis, disruption of calcium homeostasis, canalicular injury, and mitochondrial injury. 9

The most frequent mechanism of DILI is through the cytochrome P450 system metabolism, as in acetaminophen toxicity.10 The normal metabolism of lipophilic chemicals into water-soluble metabolites can be toxic in states of overdose. Phase I of the metabolic pathway involves the formation of high energy reactive intermediates which then undergo conjugation process (phase 2) that convert them to water soluble compounds that can be excreted. In dose-dependent liver injury, over dosage results in the formation of excess reactive intermediates. Subsequent covalent bonding of these reactive intermediates to necessary cellular components, such as proteins or nucleic acids, produces cellular dysfunction.9,10 Deferasirox is primarily metabolized through phase-2 conjugation. It undergoes minimal metabolism (approx. 8%) by CYP-450 system and this makes this mechanism of injury unlikely for Deferasirox.
Immune mediated liver injury is another mechanism of DILI. A chemical compound normally too small to invoke an immune response may be attached to an enzyme of sufficient size to become immunologically active. These neo-antigens can initiate both cytotoxic and humoral responses, possibly resulting in cell death. These reactions, however, are usually delayed and require multiple exposures to cause a reaction which again goes against the presentation in this particular case. Because of the patient’s markedly elevated bilirubin, one must consider cholestatic injury as another possible mechanism of injury. Bile salt transport proteins in the canilicular membranes-responsible for the generation of bile-can be blocked by several chemical compounds, causing cholestasis and jaundice. However, this type of injury is not generally associated with severe liver injury. The patient’s clinical picture of acute hepatic injury with encephalopathy suggests an alternate diagnosis.

Mitochondrial injury is one of the possible mechanisms of Deferasirox-induced liver injury. Hallmark of this type of injury is microvesicular fat in hepatocytes that can evolve into macrovesicular lesions, focal necrosis, fibrosis, and cholestasis consistent with this patient’s liver biopsy. Furthermore, patients often experience non-specific symptoms of insidious onset, such as nausea, vomiting, fatigue, and weight loss, while jaundice is a late finding. Lastly, the transaminases are usually only mildly elevated, again consistent with the laboratory workup at presentation. The mitochondrial injury can also present with lactic acidosis, pancreatitis, peripheral neuropathy, and myopathy, none of which were apparent in the presented patient. Inhibition of fatty acid β oxidation is one of the several mechanisms leading to mitochondrial dysfunction. Extreme caution should be taken in using Deferasirox in patients who have underlying liver disease. As per FDA updated guidelines, serum transaminases and bilirubin should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. Dose modification or interruption of treatment should be considered for persistent or severe elevation of liver function tests. More studies are required before exact mechanism of hepatic injury by Deferasirox could be understood.

REFERENCES