Statin-induced Liver Injury with Short Latency to Onset

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Introduction

Statins can cause an increase in liver enzymes, but these elevations resolve spontaneously in 70% of patients despite continued therapy[1]. It is rare for it to cause significant, clinically apparent liver injury. The latency to the onset of liver injury had a median of 155 days, with most cases occurring around 3-4 months after initiation of statin[2]. We describe a patient with statin-induced symptomatic liver injury within one month of statin initiation.

Case Description

A middle-aged woman with past medical history of diabetes mellitus type 2, hypertension, hyperlipidemia, and recent ST-elevation myocardial infarction (STEMI) with drug eluting stent (DES) placement presented with nausea, vomiting, generalized pruritus, painless jaundice and loss of appetite for over one week. One month prior to her onset of symptoms, she was started on atorvastatin after her STEMI. Her baseline liver biochemistries were normal.

Her initial labs on presentation were significant for alkaline phosphatase 2,170 U/L, AST 456 U/L, ALT 502 U/L, total bilirubin 15.0 mg/dL and direct bilirubin 10.7 mg/dL, showing a predominantly cholestatic pattern but also with some hepatocellular injury. Atorvastatin was stopped on admission. Computed tomography imaging (Figure 1) and ultrasound (Figure 2) showed liver steatosis and cholelithiasis. No biliary dilatation was seen on magnetic resonance cholangiopancreatography. Other workup was negative, including viral markers and autoimmune studies.

Liver biopsy showed sinusoidal dilation/congestion and lymphocytic predominant portal inflammation with eosinophils and plasma cells suggestive of drug-induced liver injury (DILI). Inflammation was not significant and there was no necrosis or apoptosis noted. She was loaded with then continued on the maintenance dose of N-acetylcysteine. She was also started on ursodiol. Her hepatic function initially continued to worsen as noted by elevated total bilirubin from 15.0 mg/dL to 21.9 mg/dL and rising INR from 1.0 to 1.6, with mildly worsening mental status. She also had acute kidney injury requiring initiation of hemodialysis.

Given lack of significant recovery with supportive care, decision was made for expedited liver transplant evaluation. While waiting for transplant evaluation, she showed gradual improvement in her liver biochemistries and symptoms, and was continued on supportive care.

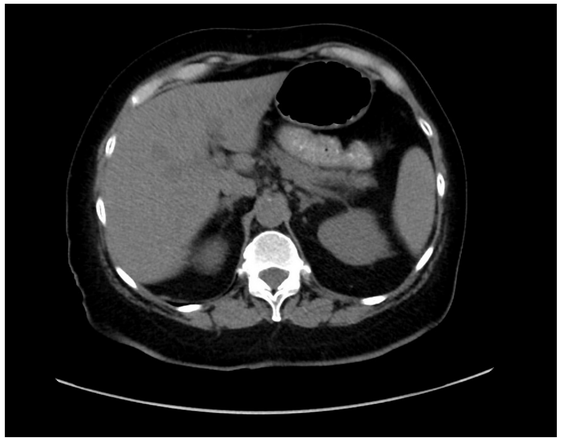

Figure 1: Abdominal CT showing liver steatosis. No biliary ductal dilatation. Cholelithiasis without CT evidence of cholecystitis

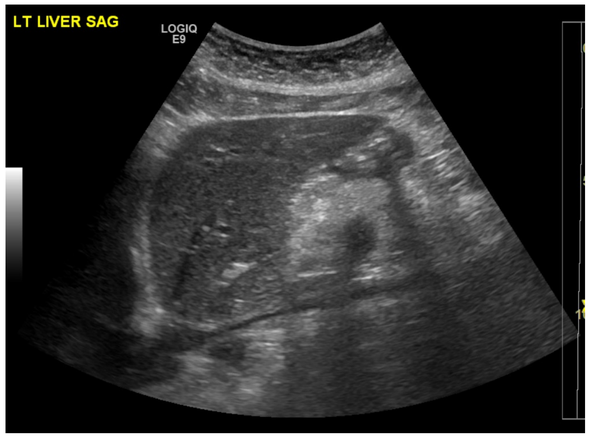

Figure 2: Abdominal US showing prominent liver with patchy steatosis. No biliary dilatation. Gallbladder with calculi and adenomyomatosis

Discussion

The HMG-CoA reductase inhibitors, statins, are among the most frequently prescribed medications worldwide. Although generally considered to be safe, statins have been associated with several side effects. In early clinical trials, elevations of aminotransferases were observed in up to 2% of patients. The incidence of statin-associated ALT elevations greater than 3 times the upper limit of normal is dose dependent and ranges from 0.5% to 3%. While generally noted in the first 3 months of statin therapy initiation, elevated aminotransferases have been observed to return to baseline in approximately 70% of patients with continued statin therapy[1].

Clinically apparent drug induced liver injury attributed to statins has been reported but appears to be rare. A 2009 systematic review of the literature identified only 40 cases of statin hepatotoxicity mostly from single case reports and no case series with more than 4 patients[2]. Among a total of 131 cases of acute liver failure due to drugs other than acetaminophen over a 10-year period, the U.S. Acute Liver Failure Study Group only reported 6 cases of acute liver failure attributed to statins[3].

The latency (time from starting statin to onset of liver injury) varied widely. Using the time to initial identification of abnormal liver tests as a definition, Russo et al. showed that latency ranged from 34 days to more than 10 years with a mean of 464 and a median of 155 days. The latency was 1 to 3 months in 6 (27%), 3 to 6 months in 6 (27%), 6 to 12 months in 5 (23%) and greater than a year in the remaining 5 (23%). No patient developed drug-induced liver injury within 4 weeks of starting the statin[4].

This case describes a patient who developed clinically significant statin-induced liver injury within one month of atorvastatin initiation. Although statins can develop mild liver-enzyme elevations, it is rare for it to cause such clinically apparent DILI. Given the widespread use of statins, this case highlights the importance for physicians to closely monitor liver enzymes in patients after initiation of statins.

References

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