

Statin-Induced Cholestatic Hepatitis: Confirmed on Rechallenge

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Although statins have been associated with an increase in serum aminotransferase levels,^{1,2} these elevations may resolve spontaneously in 70% of patients despite continued therapy and may not be associated with significant liver injury.³ Statin-induced idiosyncratic liver injury that is severe enough to cause morbidity and mortality is rare, with only a few of these cases confirmed by rechallenge.⁴ We describe a patient with statin-induced symptomatic cholestatic hepatitis that was confirmed on rechallenge.

Case Report

A white woman, age 79 years, with a history of cholecystectomy and hyperlipidemia was evaluated for new-onset painless jaundice. Statin therapy with simvastatin had been initiated for the first time 11 months prior. The patient's baseline liver biochemistries were normal. Ten months later, the patient complained of mild pruritus. Simvastatin was changed to atorvastatin. One month later, the patient presented with jaundice and increased pruritus. Physical examination was unremarkable other than mild scleral icterus. No hepatosplenomegaly or other stigmata of chronic liver disease was apparent. The patient's bilirubin level was 2.5 mg/dL, alkaline phosphatase level was 953 U/L, alanine aminotransferase (ALT) level was 307 U/L, and aspartate aminotransferase (AST) level was 123 U/L. All serologies for other causes of abnormal liver biochemistries were negative, including hepatitis A immunoglobulin (Ig) M subtype, hepatitis B surface antigen, hepatitis B core antibody IgM and IgG subtypes, hepatitis C antibody, hepatitis C RNA, Epstein-Barr virus antibodies, cytomegalovirus antibody IgM subtype, antinuclear antibody, antismooth muscle antibody, antimitochondrial antibody, antineutrophil cytoplasmic antibody, antiliver

kidney microsomal antibody, and tissue transglutaminase antibody IgA and IgG subtypes. Serum IgG, IgA, and IgM levels were normal as were the complete blood count and eosinophils. Computed tomography with contrast showed a normal liver, spleen, and bile ducts. An endoscopic retrograde cholangiopancreatography (ERCP) was normal and failed to reveal any obstructive cause of the patient's cholestasis.

Atorvastatin was discontinued, and all liver biochemistries normalized. Two months later, atorvastatin was reintroduced. Within a few weeks, the patient complained of recurrence of pruritus. The patient's alkaline phosphatase level was 783 U/L, bilirubin level was 0.6 mg/dL, ALT level was 241 U/L, and AST level was 176 U/L. Repeat imaging by computed tomography with contrast and ERCP were again normal. All liver biochemistries normalized with discontinuation of atorvastatin.

Discussion

Although rare, our case demonstrates that symptomatic cholestatic hepatitis can occur with statins. Bjornsson and colleagues reviewed statin-related drug-induced liver injury in Sweden from 1988 to 2010, including only cases in which aminotransferase levels were greater than 5 times the upper limit of normal and/or alkaline phosphatase levels were greater than 2 times the upper limit of normal.⁴ Possible statin-related drug-induced liver injury was reported in 73 cases or 1.2/100,000. Two patients died, 1 patient underwent liver transplantation, and 25 patients had jaundice. The median duration of therapy before drug-induced liver injury was 3 to 4 months (range, 30 to 248 days).

It is difficult to prove causality without rechallenge. Statin-induced liver injury, however, could only be confirmed with rechallenge in 3 of the 73 cases in the study by Bjornsson and colleagues.⁴ Rechallenge is not without risk, leading some doctors to recommend against rechallenge if significant liver injury occurs.¹ Our case adds to the literature on statin-induced idiosyncratic cholestatic

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hepatitis because of the severity of cholestasis and confirmation with rechallenge.

It is difficult to determine whether idiosyncratic liver injury caused by a statin will recur if another statin is given. In the review by Bjornsson and colleagues, 5 patients who were thought to have statin-related liver injury were given an alternate statin without recurrence of liver injury.⁴ Whether these patients did not have cross-reactivity to the alternate statin, or whether their liver injury was not due to statins in the first place, is unclear. This illustrates the greater degree of certainty achieved in confirming statin-induced idiosyncratic liver injury by rechallenge, as in our case. Pruritus with simvastatin developed in our patient. The pruritus progressed when the patient was switched to atorvastatin and recurred on rechallenge with atorvastatin, suggesting cross-reactivity.

Whereas severe idiosyncratic statin-induced liver injury is rare, mild elevations in ALT levels associated with statins are not uncommon. The incidence of statin-associated ALT elevations greater than 3 times the upper limit of normal ranges from 0.5% to 3%, is dose-dependent, and primarily occurs in the first 3 months of therapy.¹ Although many studies show that this effect is not different from placebo,³ a meta-analysis of 35 trials found an excess risk of ALT elevations of 4.2 per 1000.⁵ However, these ALT elevations may resolve spontaneously in 70% of patients despite continued therapy and may not be indicative of significant liver injury.³ This may be reflective of an adaptive response (drug tolerance).⁶ This led the US Food and Drug Administration (FDA) to revise its labeling information on statins to recommend liver function testing prior to initiation of statin therapy and to only repeat such testing for clinical indications.⁷

The occurrence of rare idiosyncratic statin-induced liver injury does not appear to be increased in patients with mild to moderately elevated ALT levels or preexisting liver disease.⁸⁻¹⁷ Studies and analyses have demonstrated that statins can be given safely to such patients.^{16,17} For example, in a retrospective cohort study of 93,106 patients with preexisting liver disease, statin exposure was, in fact, associated with a lower risk of adverse hepatic outcomes.⁸ Two studies compared 3 cohorts to evaluate statins in patients with elevated baseline ALT levels, statins in patients with normal ALT levels, and patients with elevated ALT levels who were not given statins.^{9,10} Both studies found that elevated liver enzymes do not increase the risk of hepatotoxicity from statins.^{9,10} A 36-week randomized trial of a statin or placebo in 326 patients with well-compensated chronic liver disease showed that the rate of ALT elevations in the statin group was low and did not differ from that of the placebo group.¹¹ Similarly, in a subgroup of patients with preexisting liver abnormalities who participated in a large statin

trial, no significant differences in increases in ALT levels were found between statin-treated and placebo groups.¹²

In a post hoc analysis of a randomized trial of statin therapy that evaluated 437 patients who had elevated ALT levels at baseline, 227 patients were treated with statins and compared with the 210 patients who were not.¹³ ALT levels improved in patients treated with statins ($P < .001$) with a reduction in cardiovascular morbidity ($P < .001$) compared with patients who were not treated with statins. The Liver Expert Panel of the National Lipid Association Statin Safety Task Force concluded that compensated cirrhosis and chronic liver disease should not be considered contraindications to statin therapy and that statins could be used safely in patients with nonalcoholic fatty liver disease (NAFLD).¹ Similarly, the practice guideline of the American Association for the Study of Liver Diseases concluded that statins can be used to treat dyslipidemia in patients with NAFLD and nonalcoholic steatohepatitis.¹⁶ This is important because concern for statin-induced hepatotoxicity leads to underutilization of statins despite proven indications for statin therapy.¹⁸ This is particularly relevant in hyperlipidemic patients with elevated ALT levels due to NAFLD in whom cardiovascular risks may be high.^{19,20} In contrast, statins should be avoided in patients with decompensated liver disease, acute liver failure, and cholestasis because most statins are excreted in bile, and toxic levels can develop.²¹

In summary, we report a rare case of symptomatic statin-induced cholestatic hepatitis confirmed on rechallenge. Although significant statin-induced idiosyncratic liver injury is rare, as reflected by the FDA's relabeling of recommended liver function test monitoring with statins,⁷ physicians should be aware of its occurrence.

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Review

Statins and Liver Injury

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Statins are inhibitors of hydroxymethylglutaryl coenzyme A reductase, the enzyme that catalyzes the rate-limiting step of the cholesterol biosynthetic pathway. As a class, statins are among the most frequently prescribed drugs worldwide. Lovastatin was the first statin introduced (in 1987); since then, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin (Livalo, Kowa) have been used clinically.¹ Cerivastatin was withdrawn from the market in 2001 secondary to a high risk of development of rhabdomyolysis. Statins are currently approved and used for reduction of elevated cholesterol levels and cardiovascular risk reduction. In addition, there are growing data on favorable effects of statins in dementia, hepatocellular carcinoma, and colonic neoplasia.^{2,3} Several

population-based studies have demonstrated that statin use is associated with a decreased risk of esophageal and gastric cancers.^{4,5} Statin use also has been associated with an improved response to interferon treatment for chronic hepatitis C and a reduction in portal pressure in patients with portal hypertension and metabolic syndrome.⁶⁻⁸

Clinical trials have shown that statin use has been associated with elevations in serum alanine aminotransferase (ALT) levels in approximately 3% of persons who take the drugs. Such elevations are not clinically significant in the great majority of cases; indeed, ALT levels greater than 3 times the upper limit of normal (ULN) are seen in only a small minority of patients. With continued use, the mild elevations of serum aminotransferases generally resolve. This phenomenon, which has been observed for a number of drugs, is not well understood but has been called adaptation.

Clinically important drug-induced liver injury (DILI) is very rare with statin use. Patterns of liver abnormalities seen with statins include: (1) asymptomatic elevations of ALT: usually transient and mild (ALT <3 × ULN), as already described; (2) hepatitis: with ALT >3 × ULN and clinical symptoms of liver disease; (3) cholestatic or mixed hepatitis: with development of jaundice; and (4) autoantibody-associated DILI with the presence of antinuclear antibody (ANA) and antismooth muscle antibody or antimitochondrial antibody with or without plasma cells on liver biopsy. Acute liver failure (ALF) develops in a very small minority of persons who are taking statins; indeed, the incidence is not different from that in the general population.⁹ The overall risk of DILI with statin use is estimated to be approximately 1 in 100,000 with the estimated risk of ALF being approxi-

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mately 1 in 1,000,000. Statins are often used in patients with diabetes mellitus, which itself is a risk factor for ALF. Recent analysis of the US drug-induced liver injury network (DILIN)¹⁰ database (unpublished observations) identified 22 cases of definite, highly likely, or probable statin-induced DILI. Twelve (55%) of 22 cases were predominantly hepatocellular in nature, with 10 (45%) of 22 being cholestatic or mixed.

Statins have been used in patients with underlying liver disease. Post hoc analysis from GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation study) showed a reduction in cardiovascular events in patients with nonalcoholic fatty liver disease and coronary artery disease who were treated with atorvastatin.¹¹ The cardiovascular benefit was greater in those with elevated baseline aminotransferase levels. Perhaps somewhat surprisingly, statin use was associated with a reduction in the mean serum aminotransferase levels in these patients.

A previous placebo-controlled, double-blind, randomized study established the safety and efficacy of statins in patients with well-compensated chronic liver disease. Overall, fewer patients in the statin group (pravastatin) had elevations in their serum ALT levels compared with the placebo group (7.5% vs 12.5%; $P=.13$).¹² In the same study, the subjects on the statin were less likely to have progression in hepatic fibrosis. In the cohort with nonalcoholic fatty liver disease, statin use was associated with a significant reduction in the amount of hepatic steatosis.¹³

Kerzner and colleagues describe an interesting case of statin-induced liver injury with a cholestatic pattern, reproduced on rechallenge with the same drug.¹⁴ Statins have rarely been implicated in the pathogenesis of autoimmune hepatitis–like syndrome.¹⁵ Cases with chronic DILI (abnormal liver tests for more than 6 months) had fairly high titers of autoimmune markers (ANA and antismooth muscle antibody). Causality assessment in patients with suspected DILI can be very challenging, and the differential diagnosis includes acute viral hepatitis (A, B, C, D, and E), cytomegalovirus, and herpes simplex virus (HSV). Although acute HSV seems very unlikely in the patient described by Kerzner and colleagues,¹⁴ hepatitis E was not excluded. A recent publication from the DILIN identified several cases of hepatitis E that initially had been thought to be due to DILI.¹⁶ In evaluating unexplained elevations in liver enzymes with statin use, it is also important to exclude myalgia and myositis, which may lead to increases in serum aminotransferase levels, predominantly aspartate aminotransferase levels, but with far greater increases in serum creatine phosphokinase (CPK) levels.

In summary, statins overall are safe and effective drugs with proven benefit in not only cardiovascular risk reduction but also in possibly having beneficial effects in prevention of various cancers and metabolic syndrome. Indeed,

it has been suggested that virtually all adults in developed countries should be taking statins. As a class, they have a low risk of adverse events, with benefits mostly outweighing the risks. It is recommended that liver chemistries and CPK levels be checked before initiating therapy. However, routine monitoring of liver tests while on treatment is not recommended. Rather, such testing should be performed only if there are symptoms or signs that suggest possible liver injury. In patients who develop jaundice or other systemic symptoms or signs suspected of being associated with statin use, rechallenge with the same drug is generally not recommended. After resolution of the acute injury, use of a different statin can be considered for clear indications, such as elevated serum cholesterol levels, but with careful and frequent monitoring of liver tests, especially during the first 6 months of treatment.

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