Recurrence and Severe Worsening of Hepatotoxicity After Reintroduction of Atorvastatin in Combination With Ezetimibe

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ABSTRACT: Severe hepatotoxicity is a rare but well-known adverse reaction to statins. However, despite the widespread use of statins, only a few cases describing statin reexposure or switch to another statin after liver injury have been published. The literature on hepatotoxicity with ezetimibe alone or in combination with statins is also scarce. We report a case where a patient with a history of elevated liver enzymes while using atorvastatin, but prior and subsequent good tolerance to simvastatin and pravastatin, developed drug-induced liver injury on reexposure to a combination of atorvastatin and ezetimibe. The hepatotoxicity in our patient was most likely caused by reexposure to atorvastatin, although we cannot exclude ezetimibe as a contributing factor. This case highlights the risk of hepatotoxicity recurrence on rechallenge with the same statin. The tolerance to other statins in this case also strengthens the suspicion that statin-induced liver injury may not be a class effect, although the current data are too scarce to draw any definite conclusions.

KEYWORDS: Hepatotoxicity, lipid management, statins, drug-induced liver injury (DILI), recurrence, rechallenge

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Introduction

Atorvastatin, a selective competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is a well-known and often used drug in patients in need of aggressive cholesterol-lowering and lipid-lowering therapy. It is used both in primary and secondary prevention of cardiovascular events. Some of the more frequent reported adverse reactions are muscular pain and mild elevations in serum aminotransferases.[1,2] Clinically significant hepatotoxicity is rare, estimated to occur in about 1:3000 to 1:5000 treated patients.[1] Although there might be some clinical experience in this area, only a few cases describing statin reexposure or switch to another statin after liver injury have been published.[1,3–5] This limits evidence-based decision-making regarding further lipid-lowering treatment in a patient with statin-induced liver disease. Ezetimibe is an inhibitor of intestinal absorption of cholesterol. It is used either alone or in combination with statins. The literature on hepatotoxicity with ezetimibe alone or in combination with atorva-statin is also scarce.[1,6,7] The exact mechanism behind statin or ezetimibe-induced hepatotoxicity is currently unknown.[1,8] This is as far as we know the first case report of severe hepatotoxicity following use of atorvastatin and ezetimibe in fixed-dose combination.

Case Report

The patient was a slightly overweight (body mass index: 28 kg/m^2) woman in her 70s, with hypothyroidism and hypertension for which she received levothyroxine and ramipril, respectively. In 2007, she had an ST-elevation myocardial infarction and was treated with thrombolysis and percutaneous cardiac intervention. She was also started on simvastatin 40 mg and aspirin 75 mg/d as secondary prevention against cardiovascular events. The patient had been smoking for several years but succeeded quitting after the infarction. Due to insufficient lowering of her low-density lipoprotein (LDL, 120 mg/dL), the dosage of simvastatin was increased 3 months later to 80 mg/d. An additional 5 to 6 months later, she was switched to atorvastatin 40 mg/d because of persistent LDL elevation. Between March 2009 and July 2011, the serum hepatic marker alanine aminotransferase varied between 67 and 123 U/L (upper normal limit: <45 U/L).

In January 2012, the patient was hospitalized due to a newly discovered diabetes type 2 and was started on insulin therapy. A further increase in hepatic transaminases was also noted (Table 1). At the time of hospitalization, she used atorvastatin 20 mg/d and had an LDL level of 77 mg/dL. The increase in hepatic transaminases was thought to be due to atorvastatin, which was discontinued. This resulted in a normalization of the liver enzyme levels within 2 months (Table 1). Her hypothyroidism was well controlled throughout this period.

In May 2012, her LDL cholesterol was 178 mg/dL. She was subsequently started on pravastatin 40 mg/d, without any adverse effect on hepatic markers and with a lowering of LDL to 97 mg/dL. In the beginning of June 2015, her LDL level had increased slightly to 116 mg/dL. Her general practitioner (GP) then switched her from pravastatin to Atozet (ezetimibe 10 mg in combination with atorvastatin 20 mg, once daily). After nearly 2 months, she was hospitalized with diffuse body pain, urticarial rash on her legs, loss of muscular strength, fatigue,

Table 1. Timeline of selected laboratory values.

BLOOD SAMPLE	TIME PERIOD 2009-2011	HOSPITALIZATION 2012	TWO MONTHS AFTER DISCHARGE 2012	HOSPITALIZATION JULY 2015	NOVEMBER 2015	REFERENCE VALUE
Bilirubin, mg/dL	1.8–2.1	1.9		4.3–4.7	1.2	0.3–1.5
ALT, U/L	67–123	365	40	2003–2715	38	<45
GT, U/L	42–69	295		745–805	32	<75
ALP, U/L	80–81	139		164–198	65	<105
Pancreatic amylase, U/L	68–82	64		123–125	68	10–65
Lipase, U/L		179		246–345		<300
AST, U/L		152	26	1224–2142	28	<35
INR				1.3		<1.2
Albumin, g/dL				3.9–4.0		3.4–4.5

Abbreviations: ALP, alkali phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GT, gamma-glutamyltransferase; INR, international normalized ratio.

discomfort in her chest, and nausea, but no fever. A new cardiac event was suspected, but neither repeated electrocardiograms nor cardiac markers in serum could confirm this. There was also no evidence of rhabdomyolysis or bacterial infection, and her thyroid hormone levels were normal. On admission, there were no comments regarding jaundice, but levels of hepatic markers were severely elevated (Table 1). There was also a slight increase in pancreatic enzyme levels. The patient had no history of drug or alcohol abuse or other risk-associated behavior. The LDL level was 35 mg/dL, well below the recommended target level of LDL < 70 mg/dL. Tests for autoimmune and viral hepatitis were all negative. Ultrasound examination of her liver showed no significant pathology. She denied any recent use of over-the-counter drugs or herbal supplements.

Due to her prior history of hepatic reaction while using atorvastatin, Atozet was discontinued on hospital admission. Liver biopsy was considered but not indicated as the levels of hepatic markers rapidly improved after discontinuing Atozet. The albumin level was normal during hospitalization and international normalized ratio (INR) just mildly elevated to a maximum of 1.3, which indicated that liver function was adequately preserved. Treatment with corticosteroids was not necessary. She was hospitalized for 7 days.

The final diagnosis was drug-induced liver injury (DILI) without liver failure. Regular follow-ups by her GP were arranged, and she was told not to start treatment with a new statin before normalization of all her hepatic markers. Hepatic transaminases normalized in November 2015, 4 months after discontinuing Atozet (Table 1). In February 2016, pravastatin 40 mg daily was initiated, without any reported adverse events at the last follow-up about 10 months later.

Discussion

This case report describes a patient with a previous medical history of hepatotoxicity probably due to atorvastatin. The levels of serum transaminases normalized on discontinuation of atorvastatin, and the patient subsequently tolerated pravastatin for several years without signs of hepatotoxicity. The patient had initially also tolerated simvastatin for a period of 8 months, before switching to atorvastatin. Nevertheless, nearly 2 months after reexposure to atorvastatin in combination with ezetimibe, the patient presented with significant DILI. Pravastatin was again subsequently tolerated.

Clinically significant hepatotoxicity has been reported for all marketed statins, both in case reports and adverse reaction register studies. Atorvastatin has been the most frequently implicated statin, and only a few cases with pravastatin have been published.[2–5] Whether this simply reflects the pattern of drug consumption or an actual difference in risk is currently unknown. The exact incidence of clinically significant hepatotoxicity due to statins is also unknown. Restricted sample size and study length limits the ability to detect infrequent adverse reaction during premarketing clinical trials, and patients with known risk factors for liver disease have generally been excluded from these trials. There is also a large degree of underreporting of adverse reactions through the spontaneous reporting system after marketing. Nevertheless, the available data indicate that hepatotoxicity is a rare but potentially severe adverse reaction of atorvastatin and other statins.[5,9]

Statin-induced hepatotoxicity most commonly occurs within the first 3 to 4 months of therapy, but cases with prolonged latency for up to 10 years have been reported.[4,5] The pattern of injury varies from markedly hepatocellular to distinctly cholestatic or a mix of the two. Statins are also considered able to trigger an autoimmune hepatitis in predisposed patients,[1,4,10] but the presentation and rapid lowering of transaminases after discontinuing the suspected drug suggest that this was not the case in our patient. The exact mechanism behind hepatotoxicity due to statins is currently unknown.[1]

The rates of transaminase elevations have not been higher with ezetimibe monotherapy compared with placebo, but when

used in combination with statin, the rates of transaminase elevations have been slightly elevated. Clinically apparent acute liver injury has been reported, but is rare, and because ezetimibe often is used in combination with statins, the role of ezetimibe has been difficult to assess.[1] However, a few case reports describe ezetimibe-induced hepatotoxicity without concomitant or recent use of statins.[6,7]

A small number of case reports of DILI suspected to be due to the concomitant use of ezetimibe and statins have been published, and only 3 for the concomitant use of ezetimibe and atorvastatin, none of which involved a fixed-dose combination. In these prior case reports, the patients had used atorvastatin for more than a year, and hepatotoxicity first appeared a few months after ezetimibe was added. Unlike in our patient, there is no mentioning of previously elevated liver enzyme levels with atorvastatin monotherapy. Ezetimibe was thus the most likely triggering factor in these previous cases, but a possible role for atorvastatin alone or in combination with ezetimibe could not be excluded.[8,10] Our patient had previously experienced elevated transaminase levels while using atorvastatin, with improvement after withdrawal. Atorvastatin was thus the most likely cause of the hepatic injury in our patient. It is possible, though, that ezetimibe acted as a catalyzing factor of DILI in this patient vulnerable to atorvastatin.

In our patient, atorvastatin in monotherapy resulted in LDL cholesterol of 77 mg/dL (2012). Atorvastatin in combination with ezetimibe (2015) resulted in an LDL value of 35 mg/dL. Such a low LDL level may be the result of emerging liver failure, but the albumin level was normal, and INR only slightly elevated. The low LDL level was thus more likely due to the powerful lipid-lowering effect of the drug combination.[11,12]

This case was reported to the Norwegian Regional Pharmacovigilance Centre (RELIS) in accordance with national guidelines. The assessment on whether a reaction or a symptom is a result of disease or an adverse drug effect is often based on the clinical judgment of physicians, and this will affect the probability of the event to be reported. Adverse drug effects are usually categorized as definite, probable, possible, or doubtful according to a previously described system (the Naranjo probability scale). For DILI, specific causality scales have been developed, for example, the Roussel Uclaf Causality Assessment Method (RUCAM).[1] The exclusion of other common causes for hepatitis and the recurrence of hepatotoxicity on rechallenge with atorvastatin strengthen the suspicion of a causal relationship in our case. Using the above-mentioned causality scales, it is probable or highly probable that the DILI in our patient was caused by exposure to atorvastatin (Naranjo score: 6; RUCAM score: 9-10). However, as stated, we cannot exclude ezetimibe as a contributing factor. Our patient also developed diabetes while using statin. Although statin therapy has been linked to a possible increased risk of developing new onset diabetes,[13] any causal relationship in this particular case is impossible to determine.

The risk of severe DILI due to statins has not been proven to be dose related. Nevertheless, a generally "start low, go slow" strategy can be recommended in statin-naive patients. The experience with reexposure to statins after suspected statin-induced hepatotoxicity is limited, but recurrence of injury on rechallenge with the same statin has been reported.[1,3-5,9] Rechallenge is therefore not recommended,[1] and this case highlights that physician should remember that this also applies to combination products. Whether switching to another statin after DILI is safe is not well documented, but some authors report that this has been successfully done in a few cases without signs of hepatotoxicity. For instance, single reports of a safe switch to pravastatin or simvastatin after atorvastatin-induced liver injury or to simvastatin or atorvastatin after rosuvastatin-induced liver injury have been published.[3,5] This indicates that statin-induced DILI may not be a class effect, but the published data are currently too scarce to draw any definite conclusions. Rare instances of recurrence of hepatotoxicity after switching to another statin have also been reported, for example, when switching from fluvastatin to atorvastatin in one patient.[3] A switch must therefore be carefully monitored through blood samples and clinical examination.

Our patient had an urticarial rash at the time of hospitalization. It has been speculated that in some cases statin-induced DILI could have an immunologic component.[1] If this is the case, it seems reasonable to avoid statins with a molecular structure similar to the culprit drug. Simvastatin, lovastatin, and pravastatin exhibit close structural homology and are often called type 1 statins, whereas atorvastatin belong to the type 2 statins together with fluvastatin and rosuvastatin.[14] This fits well with the fact that our patient tolerated simvastatin and pravastatin, but not atorvastatin. This also fits well with some, but not all, of the few earlier referred cases with experience from switching statins. We cannot, however, exclude that this is a coincidence, and that the apparent selective intolerance in our and these other patients is due to other drug characteristics.

Conclusions

This case contributes to the currently limited documentation regarding the risk of recurrence of hepatotoxicity on rechallenge with the same statin and the possible tolerance to other statins. The liver injury in our patient was most likely caused by reexposure to atorvastatin, although we cannot exclude that ezetimibe was involved. Our patient has subsequently now used pravastatin for 10 months with no reported adverse events. Together with the fact that she previously tolerated pravastatin and simvastatin, this case strengthens the suspicion that DILI due to statins may not be a class effect. Thus, if statin-induced liver injury is suspected in a patient with a strong indication for lipid-lowering therapy, a carefully monitored switch to another statin could be considered.

Author Contributions

SBE designed and drafted the paper. EN and KTL revised the paper. All authors approved the final version.

Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The patient has signed an official consent form for participating in this case report and for us to publish it.

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