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doi:10.3748/wjg.14.5098

World J Gastroenterol 2008 August 28; 14(32): 5098-5099
World Journal of Gastroenterology ISSN 1007-9327

CASE REPORT

Serious drug-induced liver disease secondary to ezetimibe

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Received: May 15, 2008 Revised: June 23, 2008
Accepted: June 30, 2008
Published online: August 28, 2008

Abstract

Ezetimibe is the first member of a new family of lipid-lowering drugs that inhibits uptake of dietary and biliary cholesterol. It was approved by the FDA in 2002 for hypercholesterolemia alone or in combination with statins. Its use has been spreading over the last years. Ezetimibe was considered a safe drug. We report a case of a woman who developed a serious hepatocellular drug-induced liver disease after 4 mo therapy with 10 mg daily of ezetimibe. After withdrawal of the drug, the patient recovered slowly. Ezetimibe may produce serious toxic hepatitis and prompt withdrawal is mandatory in case of a significant abnormality in liver testing after beginning or during treatment with ezetimibe.

Key words: Ezetimibe; Hepatitis; Drug-induced liver disease

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Castellote J, Ariza J, Rota R, Girbau A, Xiol X. Serious drug-induced liver disease secondary to ezetimibe. *World J Gastroenterol* 2008; 14(32): 5098-5099 Available from: URL: http://www.wjgnet.com/1007-9327/14/5098.asp DOI: http://dx.doi.org/10.3748/wjg.14.5098

INTRODUCTION

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol. It was approved by the FDA in 2002 for hypercholesterolemia alone or associated with statins. Since then, the use of ezetimibe has increased, especially in the United States[1]. Some guidelines suggest that ezetimibe may become the first choice for patients who do not tolerate statins[2]. Randomized clinical trials showed that ezetimibe caused significant liver function abnormalities in 1% of the treatment group. These changes were asymptomatic and entirely reversible. We report a case of serious hepatitis secondary to ezetimibe.

CASE REPORT

A 56-year-old woman was admitted because of painless jaundice and pruritus. Her past medical history revealed essential hypertension, uterine myoma and a hiatal hernia. She never consumed more than 1 alcoholic drink per day. In the last three years, her medication was unchanged and consisted of bisoprolol 10 mg/d and omeprazol 20 mg/d. Because of persistent hypercholesterolemia, her family doctor prescribed ezetimibe 10 mg/d for 4 mo before admission. She was referred to our unit because of apparition of jaundice, a progressive scretching and liver test abnormalities.

At physical exam, there was intense jaundice and some scraping lesions. Her liver was not palpable and there were no further abnormalities. Laboratory investigation showed the following results: aspartate transaminase, 16.64 kat/L (normal, < 0.5 μkat/L); alanine transaminase, 26.26 μkat/L (normal, < 0.56 μkat/L); γ-glutamyl transferase, 1.15 μkat/L (normal, < 0.43 μkat/L); alkaline phosphatase, 1.9 μkat/L (normal, < 1.5 μkat/L); total bilirubin, 602 μmol/L (normal, < 18 μmol/L). Blood count, prothrombin time and kidney function test were normal. Viral serology tests were negative (hepatitis A, B, C, Epstein-Barr virus, Herpes virus, HIV and cytomegalovirus). Autoimmune serology (antinuclear, antimitochondrial, anti-liver-kidney microsomal and anti-smooth muscle) was all negative. At ultrasonography, the liver showed no abnormality and biliary obstruction was disclosed.

Ezetimibe was stopped. Jaundice and pruritus improved slowly as well as laboratory results. Four weeks later a laboratory exam was completely normal.

DISCUSSION

The temporal association, the improvement after

cessation of the drug and the exclusion of alternative possible causes permit us to diagnose ezetimibe-induced hepatotoxicity with confidence. Although rechallenge with the same drug could give us a definitive diagnosis, the clinical severity of the hepatitis made us exclude this possibility. Liver biopsy can suggest hepatotoxicity or exclude alternative diagnoses but it was not performed in this case.

Ezetimibe does not affect the cytochrome P450 system; it undergoes extensive glucuronidation in the wall of the small intestine and liver to form the active metabolite ezetimibe glucuronide. Ezetimibe does not induce or inhibit enzyme systems in the liver but undergoes enterohepatic circulation and is exposed to the liver and bile.

Statins rarely cause clinically significant liver injury, although asymptomatic elevations in aminotransferases are common. It has been suggested that this laboratory abnormality may result from muscle damage and not by hepatic injury[3]. Ezetimibe does not interfere with plasma levels of HMG-coA reductase inhibitors such as atorvastatin and simvastatin. Association of ezetimibe and statins does not lead to an apparent increase of hepatic side effects. Ezetimibe was expected to be even less hepatotoxic than statins and has been considered a safe drug. Nevertheless, it should be kept in mind that in a newly marketed drug, finding hepatotoxicity with an incidence of 1:10 000 (the approximate incidence of most idiosyncratic reactions) would require 30 000 patients treated with this drug[4].

The pattern of drug-related liver injury can be classified in hepatocellular, cholestatic or mixed according to laboratory data[5]. Until now, four cases of significant drug-induced liver injury associated with ezetimibe have been reported[6-8], three of them associated with atorvastatin. One case was a cholestatic type, another one was hepatocellular and the last two were drug-induced acute autoimmune hepatitis. Our patient presented as serious hepatocellular hepatitis[9]. Patients with acute toxic hepatocellular damage are at high risk of acute liver failure. Mortality, or its surrogate marker, liver transplantation, is superior to 10%; this is known as "Hy's rule".

Although causes of ezetimibe toxicity are unclear, apart from an idiosyncratic drug reaction, it could be hypothesized that a conjugation defect leads to accumulation of toxic levels of ezetimibe or their metabolites. As hepatotoxicity by ezetimibe has been reported in different types according to laboratory data, several mechanisms may be implied.

The current recommendation to monitor liver function after beginning therapy with statins is controversial with some experts calling for its re-examination. Ezetimibe, alone or associated to statins, may produce serious toxic hepatitis. Caution should be taken and the necessity of analytical follow-up after beginning or during the treatment with ezetimibe is unknown. A prompt withdrawal of the drug is mandatory in case of a significant abnormality in liver tests.

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S- Editor Zhong XY **L- Editor** Ma JY **E- Editor** Ma WH