Hepatotoxicity associated with statins: Role of drug interactions

Dear Editor,

Diagnosis of drug-induced liver injury (DILI) remains a challenge, partially due to the fact that drugs may present different hepatotoxic potential depending on the interplay of host factors, pharmacological properties, and the environment.

In the current issue of JAPS, Thotakura et al. (2018) present an atorvastatin-induced hepatotoxicity clinical case and suggest that hepatotoxicity mechanism might be accelerated due to clopidogrel use. Statins are being increasingly recognized as beneficial for a variety of liver disorders, including cirrhosis and portal hypertension in animal models and even have been suggested to protect from acute liver failure in patients with DILI (Robles-Diaz et al., 2014). However, statins have also been identified as agents incriminated in hepatotoxic reactions. The authors referred a few cases of idiosyncratic liver injury with statins but there are more cases described in the literature. Eleven cases of statin-related DILI were reported by the Spanish DILI Registry until 2005 (Andrade et al., 2005) and the total statin DILI cases reached to 47 until 2014 (Perdices et al., 2014). In Sweden, between 1988 and 2010, a total of 73 cases were included in the SADRAC database (Björnsson et al., 2012). The vast majority of reports of statin-induced hepatotoxicity were due to atorvastatin, and a higher proportion of patients had the hepatocellular type of liver injury.

Difficulties in how to apply the scale are a serious setback and none of the risk factors focused on the Council for International Organizations of Medical Sciences (CIOMS) scale has been proven to play a conclusive role in determining hepatotoxicity causality (García-Cortés et al., 2011). Moreover, the CIOMS scale has some limitations, such as causality of two drugs taken with the same temporal sequence cannot be distinguished, especially if both drugs exhibit the same hepatotoxic potential. However, in this case reported atorvastatin withdrawal was followed by a rapid normalization in the liver profile, which supports the role of atorvastatin in the hepatic injury.

The risk of idiosyncratic DILI due to statins has not been proven to be dose-dependent (Chen et al., 2015) but an association between daily dose and poor DILI outcome exists and the evidence suggest that surpassing a threshold dose is associated with an increased risk of triggering liver injury among the treated patients (Lammert et al., 2008). In 2014, Carrascosa et al. (2014) reported a patient treated with atorvastatin at a standard therapeutic dose who developed acute liver failure after doubling the daily dose of the drug. The authors mentioned that clopidogrel acted as a catalyzing factor of DILI in this patient vulnerable to atorvastatin, but the role of this drug is difficult to assess. The authors speculate that clopidogrel had a synergistic effect on atorvastatin that ultimately led to liver injury but the proposed mechanism is not clearly presented. Both clopidogrel and atorvastatin are metabolized by CYP450. We consider that negative drug-drug interactions, due to clopidogrel irreversibly inhibiting CYP450 may cause an increase in the plasma concentrations of statins that exceed a given threshold dose resulting in liver injury.

In conclusion, the potential of a drug interaction between atorvastatin and clopidogrel in triggering hepatotoxicity need to be confirmed but the study by Thotakura et al. may encourage DILI investigators to assess the role of drug interactions in idiosyncratic drug-induced liver injury, particularly when more than one drug could be responsible.

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