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LETTER TO THE EDITOR

Statins in liver cirrhosis in a developing country: benefits overweigh the risk?

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Dear Editor,

We have read with great interest the article published by Mulchandani R [1], where a complete review of the adverse effects associated with statins is carried out, which is affected by factors such as genetic and ethnic variations, lipophilicity of the drug, interaction medications, and preexisting medical conditions. Although it is known that the benefits of statins outweigh the risks, hepatotoxicity is considered as the main concern regarding their use in clinical practice.

Statins are lipid-lowering drugs that, by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, decrease cholesterol production [2].

The main indication lies in the primary and secondary prevention of coronary heart disease [3]. They have pleiotropic effects due to a reduction in isoprenylation of proteins that inhibit GTP-binding proteins involved in the transduction of extracellular stimuli to intracellular pathways [2], including the modulation of immune responses, the improvement of anti-inflammatory processes, and their alterations of the signaling pathways that involve cholesterol intermediaries [3]. The benefit of these pleiotropic effects has also been seen in stroke, cancer, chronic lung disease, metabolic-associated fatty liver disease (MAFLD), and liver cirrhosis [3,4]

Liver cirrhosis is the final stage of a liver fibrosis process, almost always irreversible, making the patient susceptible to the adverse effects of some medications. Although chronic infection by the Hepatitis C virus and alcoholic liver disease are important causes of liver cirrhosis in many countries [5], including ours; according to the national reports [6], the Fatty liver disease (NAFLD) now called MAFLD due to its association with metabolic dysfunction, has become increasingly common [5,7]; this is perhaps due to an increase in their diagnosis, as well as the effect of vaccination and new treatments for hepatitis B and C, respectively.

Previously, statins were a relative contraindication in patients with chronic liver disease due to their potential hepatotoxicity and the possibility of worsening the course of liver disease, as well as requiring periodic monitoring of liver functions. For example, in Peru, clinical practice guidelines still recommended to monitor transaminases at the beginning of treatment, at 3 months, and after a year; it is also recommended to not routinely exclude people with elevations of liver transaminases less than 3 times the upper limit of normal from statin therapy [8]. However, slight increases in transaminases have not been shown to indicate proper hepatotoxicity or impaired liver function. Furthermore, progression to cirrhosis or liver failure is extremely rare, which is why systematic monitoring of transaminases should no longer be recommended during statin treatment [9].

Currently, studies have shown multiple benefits in patients with advanced chronic liver disease, such as the decrease in portal pressure, improvement of the hepatic sinusoidal endothelium and hepatic microvascular dysfunction, reduction of fibrogenesis, protection against ischemia and reperfusion injury, reduction in the sensitivity to endotoxin-mediated liver damage, prevention of liver injury due to hypovolemic shock and delay in the progression to cirrhosis of any etiology [10]. The reduction in portal pressure is caused by the increase in nitric oxide in the hepatic circulation, decreasing the resistance and therefore the portal pressure. It is postulated that in the long term, simvastatin may cause this latter effect, despite the fact that no significant reduction in the hepatic venous pressure gradient has been found. Likewise, they induce the expression of the transcription factor KFL2, involved in apoptosis, inflammation, oxidative stress, thrombosis, and vasodilation; in this way, it regulates the expression of vasoprotective genes, improving the functionality of endothelial cells. The BLEEPS study demonstrated that the use of 40 mg of simvastatin for 2 years significantly improves survival, mainly related to the risk of bleeding and infection, in patients with liver cirrhosis [11]. A meta-analysis suggests that statins have a protective effect against hepatocarcinoma, probably due to the prevention of progression to cirrhosis, an effect apparently limited to lipophilic statins such as atorvastatin and simvastatin [10]. Statins probably also reduce the risk of fibrosis in MAFLD and nonalcoholic steatohepatitis, in addition to having a beneficial effect on dyslipidemia and the prevention of cardiovascular events in these patients [10].

Hepatotoxicity due to statin use is often dose related. The latency period of liver injury is variable; it can occur after

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6 months or even up to 10 years after starting statin treatment [10,12]. Atorvastatin hypertransaminemia occurs in 0.3%, which increases up to 2.3% in patients receiving high doses (≥80 mg), may cause significant liver toxicity in 1 of 3000–5000 users, usually showing a mixed pattern, whereas the hepatocellular pattern is more common with simvastatin [10]. The prognosis of statin-associated liver injury is generally considered favorable for most patients, whereas deaths due to atorvastatin and simvastatin have rarely been reported [13].

In an attempt to solve the problem of statin use in patients with chronic liver disease, the recommendations of the National Lipid Association Statin Liver Safety Task Force state that compensated cirrhosis of the liver is not a contraindication to the use of statins and that mild increase of liver enzymes should not be considered an impediment for the initiation or continued use of these. However, decompensated cirrhosis or acute liver failure remains an absolute contraindication [14].

Finally, there is a lot of evidence in favor of the use of simvastatin, in patients with liver cirrhosis, thereby outweighing the risks that we previously feared. We encourage its implementation as part of the comprehensive management of all patients with compensated liver cirrhosis, an important cause of morbidity and mortality in Peru and many other countries, wherein its prevalence is increasing together with obesity and MAFLD.

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Declaration of interest

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