Reviewer #1:

My comments:

*table1: the phrase of "In Bold Drugs of Clinical use in Argentina " should be omitted, and table should be modified accordingly.

Answer: Done, page 32.

Previous

Table 1. Simvastatin-Drugs Interactions: Warning Levels and Usage Recommendations [27]. In Bold Drugs of Clinical use in Argentina

Now

Supplementary Table 1. Simvastatin-Drugs Interactions: Warning Levels and Usage Recommendations

*the section titled as "our experience" should be extensively shortened. Whether the data was or was not published before must be stated. If the data was not published before, this section must be omitted, and submitted as another manuscript.

Answer: Done, pages 20 and 21.

Previous

OUR EXPERIENCE

The high mortality rate of decompensated cirrhosis underlines the need for new treatments. Experimental models of cirrhosis and its reported relationship with atherosclerotic cardiovascular disease have provided data supporting the rational use of statins in these patients. However, little is known about the safety of statins in this setting. We evaluate the safety of chronic simvastatin treatment in patients with decompensated cirrhosis. We conducted a prospective, open, uncontrolled, phase 2a trial in 30 patients with CTP class A (n = 6), B (n = 22), and C (n = 2) decompensated cirrhosis. The patients received standard treatment throughout the trial plus simvastatin 20 mg/day for 2 weeks, and after that, simvastatin 40 mg/day up to 1 year [67].

Muscle injury was assessed according to the National Lipid Association Safety Expert Panel of the US [36]. It was observed in eleven out of thirty patients (36%), seven developed myalgia (23.4%), and four myonecrosis (13.3%). All of them were related to simvastatin. Furthermore, the association between muscle injury or no muscle injury and cirrhosis severity was analyzed through CTP class, CTP score, and MELD score. A significantly greater baseline MELD score was observed within the group with muscle injury 14.0 ± 3.6 than the group without muscle injury 11.4 ± 2.8 (P = 0.035). Moreover, the only two CTP class C patients included in the study developed myonecrosis, and the other two patients with myonecrosis were CTP class B. When comparing the group without muscle injury versus the group with muscle injury, a significant improvement in CTP class A 63%, B 37% and C 0% versus A 27%, B 55% and C 18%, respectively (P = 0.020) and a lower value of CTP score 6.3 ± 1.3 versus 7.6 ± 1.9, respectively (P = 0.030) were found at the end of the trial. Thereon, the receiver operating characteristic (ROC) analysis revealed a cutoff value > 12 for baseline MELD score to differentiate patients with muscle injury from patients without muscle injury, with a sensitivity of 72.7%, the specificity of 73.7%, and area under the ROC curve of 0.73. Besides, a cutoff value ≤ 6 for end-of-trial CTP score to differentiate patients without muscle injury from patients with muscle injury, with sensitivity of 63.2%, specificity of 72.7%, and area under the ROC the curve of 0.71. Cirrhosis has a significant impact on statin pharmacokinetics [29] (See, Safety, Reduced activities in statins metabolism and/or transport).

No patient developed liver injury evaluated through the definition and phenotype standardization of drug-induced liver injury in patients with previous liver injury proposed by Aithal et al. [68].

We used the American Diabetes Association criteria for diagnosed new-onset diabetes mellitus (DM) [69]. Only one patient developed DM (3.3%). This rate is more significant than reported in the JUPITER trial (0.6%), the first trial to observe an increase in DM [70].

Gastrointestinal symptoms recorded were 53.3% of patients. The rate of each of them was from 7% to 40%. Many patients had more than one symptom. This figure is more significant than reported with simvastatin in subjects without liver disease, for all digestive symptoms, 10%, and each one of them from 0.7% to 2.5% [17].

Simvastatin dosage was reduced by myalgia or transiently interrupted due to myonecrosis; for this reason, muscle injury was considered the only clinically significant adverse event. No patient required permanent discontinuation of simvastatin for severe liver injury, clinical rhabdomyolysis, or any other serious adverse event.

In conclusion, chronic simvastatin treatment in patients with decompensated cirrhosis up to 1 year was associated with a high frequency of adverse events, although no liver injury was registered. Moreover, simvastatin dosage modification was only necessary to alleviate muscle injury, which in turn appears to be related to simvastatin dose and severity of cirrhosis. Consequently, simvastatin 40 mg/day should not be prescribed in patients with cirrhosis MELD score > 12 because of a high rate of adverse muscle events or in CTP class C patients due to potential severe muscle injury.

Now

OUR EXPERIENCE

A safety prospective, open, uncontrolled phase IIa trial was recently published online ahead of print. It was about chronic simvastatin treatment in patients with decompensated cirrhosis. This trial included 30 patients, CTP class A (n = 6), B (n = 22), and C (n = 2). The patients received standard treatment plus simvastatin 20 mg/day for 2 weeks, and after that, simvastatin 40 mg/day up to 1 year [68].

Muscle injury was assessed according to the National Lipid Association Safety Expert Panel of the US [36]: 11 out of 30 patients (36%) developed muscle injury, of which 7 developed myalgia (23.4%), and the remaining 4 myonecrosis (13.3%). All of them were related to simvastatin. On the other hand, a significantly greater

baseline MELD score was observed within the group with muscle injury 14.0 ± 3.6 than the group without muscle injury 11.4 ± 2.8 (P = 0.035). The receiver operating characteristic analysis revealed a cutoff value > 12 for baseline MELD score to differentiate patients with muscle injury from those without muscle injury. Moreover, the only two CTP class C patients included in the study developed myonecrosis.

No patient developed drug-induced liver injury drug-induced liver injury according to the criteria proposed by Aithal et al. [68].

One patient developed DM (3.3%). This rate is more significant than for the first time reported in the JUPITER trial (0.6%) [69].

Gastrointestinal symptoms were recorded in 53.3% of patients. The rate of each of them was from 7% to 40%. This figure is more significant than reported with simvastatin in subjects without liver disease, for all digestive symptoms, 10%, and reach one of them from 0.7% to 2.5% [17].

Simvastatin dosage was reduced exclusively by myalgia and transiently interrupted due to myonecrosis; for this reason, muscle injury was considered the only clinically significant adverse event.

In conclusion, chronic treatment with simvastatin 40 mg/day in patients with decompensated cirrhosis up to 1 year was associated with several adverse events, although no liver injury was registered. Moreover, muscle injury was the only clinically significant adverse event, which appears to be related to the simvastatin dosage and the degree of cirrhosis severity. Consequently, simvastatin 40 mg/day should not be prescribed in patients with cirrhosis MELD score > 12 because of a high rate of adverse muscle events and in CTP class C patients due to potential severe muscle injury.

* the manuscript must be edited for the grammar and format. Some parts of editing can be found in the attached file.

Answer:

Previous

Tables 1, 2, and 3.

Figures 1 and 2.

Now

Tables 1 and 2.

Supplementary: Table 1 and Figures 1 and 2.

Reviewer #2:

Major: The author classified the effectiveness of statins into observational studies and randomized controlled studies to explain, but in the following description, they classified according to the occurrence of infection and hepatocellular carcinoma. We hope that the author can classify and elaborate according to different ending points (such as portal pressure, complications including (bleeding, SBP, etc..), risk of cirrhosis decompensation, and risk of death….).

Answer: Done, pages 12 to 18.

Previous

Observational studies

Randomized controlled trials

A prospective, open and uncontrolled trial

Statins and infections in cirrhosis

Statins and hepatocellular carcinoma

Now

Statins and risk of cirrhosis decompensation, and mortality

Statins and portal hypertension

Statins and risk of infections

Statins and risk of hepatocellular carcinoma

Minor: It is more appropriate to replace liver fibrosis with cirrhosis in the keywords.

Answer: Done, page 3.

Previous

Keywords: Fibrosis; Liver disease; Statins; Safety; Efficiency

Now

Keywords: Cirrhosis; Liver disease; Statins; Safety; Efficiency