



Could statins be a real therapeutic option for the treatment of hepatitis C?

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Dear Editor,

We read with interest the recent article by Malaguarnera *et al.*(1) on the reduction of non-alcoholic fatty liver disease (NAFLD) in patients receiving treatment for hepatitis C who were also treated with rosuvastatin. According to the results presented in the study, patients in the group receiving interferon, ribavirin, and rosuvastatin showed major improvements in their levels of aminotransferase, fasting glucose, insulin, and CRP and their HOMA index. Apparently, these parameters were predictors of sustained virological response (SVR) in the univariate analysis, but not in the multivariate analysis. We believe that the design of the clinical trial was adequate to eliminate potential confounding factors. Both groups were similar, and the liver tissue collected both before and after treatment allowed for an objective evaluation of steatosis in these patients.

The results found by the authors seem to be promising; however, it is clear that the main weakness of the study is that it was conducted in patients who received antiviral

treatment, leukocyte interferon alpha, which is not the standard of care for hepatitis C. At the same time, it is striking that these patients achieved such a high rate of SVR, one similar to those treated with the current combination therapy of peginterferon (Peg-INF) plus ribavirin. This could be explained because the authors analyzed the two groups (with and without rosuvastatin) without separating the patients by genotype, which is the most important factor for SVR. Currently, most studies prefer to investigate new therapies only in genotype 1 patients because they are the most difficult to treat. Another limitation one has to consider with regard to the study is that the sample size was not adequate to obtain enough power to detect a statistically significant difference.

Several studies suggest that lipid-lowering agents, i.e., inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, also known as statins, may have a potential therapeutic effect on hepatitis C. These agents could block the formation of lipid precursors by interfering with viral replication, but results of in vitro and clinical studies have yielded conflicting results. Forde *et al.* (2) conducted a longitudinal cross-sectional study investigating the effect on viral loads in 101 patients with hepatitis C who received statins. They did not find a significant change in viral replication (HCV RNA-titers) before and after treatment with statins.

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Milazzo *et al.* (3) demonstrated that the addition of fluvastatin as adjuvant therapy to Peg-INF and ribavirin in co-infected HIV/HCV genotype 1 patients improved rapid viral response (RVR) rates; however, at the end of the study period, there was no significant improvement in SVR rates. On the other hand, Sesaki *et al.* (4) investigated the efficacy of 20 mg of fluvastatin plus Peg-INF and ribavirin in a pilot study of 21 patients with genotype 1 and high viral load, where patients achieved a 67% rate of SVR. Harrison *et al.* (5) conducted a retrospective study with more than 1464 patients and found that SVR rates were higher in patients with elevated low-density lipoprotein (LDL) cholesterol levels versus those with normal LDL cholesterol levels (44.9% vs. 34.0% $P < 0.001$). In this study, 66 patients received statins prior to combination therapy with Peg-INF and ribavirin, identifying an association between statin use and improvement in SVR compared with those not receiving statins (53% vs. 39% $P = 0.02$).

Moreover, the effective management of NAFLD with statins has also been controversial. In a recent study by Foster *et al.* (6), 80 patients with NAFLD were randomized to receive atorvastatin plus vitamin C and Eversus. placebo over 3.5 years. Follow-up showed that there was a decrease in steatosis in the statin group (70% vs. 34%). Factors have also been identified which negatively impact SVR rates, including insulin resistance, advanced fibrosis, steatosis, high body mass index (BMI), advanced age, and some

polymorphisms of interferon λ3 (IL-28B), among others. Today, we know that steatosis induced by HCV is a risk factor for progression to liver fibrosis and poor response to antiviral therapy. Subsequent studies have attempted to show that statins improve aminotransferase levels as well as possibly increase SVR rates in patients with metabolic syndrome by improving insulin resistance and decreasing steatosis and LDL cholesterol levels (5).

The concern associated with the use of statins in patients with liver diseases due to potential hepatotoxicity becomes less serious. In general, hepatotoxicity associated with statins is only mild, or it is identified as asymptomatic elevation of aminotransferase levels. In patients with NAFLD, aminotransferase levels tend to return to normal levels with the improvement of dyslipidemia following treatment with statins. An aspect to consider about statin use are some adverse effects such as myalgia and skeletal muscle weakness; in the study of Malaguarnera *et al.* (1), myalgia was present in a higher proportion of patients in the statin group (55% vs. 30%). The elevation of creatine kinase (CK) levels and rhabdomyolysis are also isolated reported side effects (7). In the future, it would be beneficial to conduct multicenter prospective randomized double-blind placebo-controlled trials with large samples of patients to investigate whether there is a real benefit from statins as adjuvant therapy in patients with hepatitis C.

Authors' reply to: Could statins be a real therapeutic option for the treatment of hepatitis C?

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Dear Editor,

We appreciate the comments of Mendez-Navarro *et al.* (8) to our article on the reduction of nonalcoholic fatty liver disease (NAFLD) in chronic hepatitis C patients treated with leukocyte interferon (IFN)- α 3 times per week for 12 months plus daily oral ribavirin with or without rosuvastatin (1). The unsatisfactory result in sustained virological response (SVR) in hepatitis C virus (HCV) genotype 1 carriers requires the identification of novel compounds with antiviral activity against HCV as protease and polymerase inhibitors, or against host enzymes necessary for viral replication (3). Serum low-density lipoprotein (LDL) levels have been identified as prognostic factor of SVR to IFN-based treatment in patients with HCV infection (9), suggesting that statins might favor HCV entry into hepatocytes which translates into higher viral loads. IFN- α induces a reduction of serum high-density lipoprotein (HDL) levels as well as an increase in triglycerides levels and, consequently, the amount of fat in the liver. The accumulation of fat, including free fatty acids, may be the result of increased mobilization from other tissues and increased synthesis of free fatty acids by hepatocytes. The current standard treatment for hepatitis C is the combination of pegylated IFN (Peg-INF) with ribavirin. Moreover, statin treatment in patients with HCV represents an "oxymoron". In fact, statins can reduce viral load, LDL cholesterol levels, and triglyceride levels in patients with NAFLD, thus preventing liver fibrosis; on the other hand, a very common side effect of statin treatment is represented by an increase in transaminase levels (10). Furthermore, statins can cause muscle-related side effects that are also common in patients treated with IFN alone. In our study, we noted that administration of rosuvastatin decreased LDL cholesterol and triglyceride levels, increased HDL cholesterol levels, and may reduce HCV replication and steatosis. We evaluated all these aspects when choosing the most appropriate IFN treatment. We used leukocyte IFN- α which, in our opinion, is well tolerated, with only a small percentage of adverse events related to the drug (11, 12). Furthermore, we used IFN because of its shorter half-life compared to Peg-INF, thus reducing the

dropout rate of patients. Large prospective randomized studies are necessary to validate our findings in terms of improvement of the current standard protocol efficacy and adverse events.

References

1. Malaguarnera M, Vacante M, Russo C, Gargante MP, Giordano M, Bertino G, et al. Rosuvastatin reduces nonalcoholic fatty liver disease in patients with chronic hepatitis C treated with α -interferon and ribavirin. *Hepat Mon.* 2011;11(2):92-8.
2. Forde KA, Law C, O'Flynn R, Kaplan DE. Do statins reduce hepatitis C RNA titers during routine clinical use? *World J Gastroenterol.* 2009;15(40):5020-7.
3. Milazzo L, Caramma I, Mazzali C, Cesari M, Olivetti M, Galli M, et al. Fluvastatin as an adjuvant to pegylated interferon and ribavirin in HIV/hepatitis C virus genotype 1 co-infected patients: an open-label randomized controlled study. *J Antimicrob Chemother.* 2010;65(4):735-40.
4. Sezaki H, Suzuki F, Akuta N, Yatsuji H, Hosaka T, Kobayashi M, et al. An open pilot study exploring the efficacy of fluvastatin, pegylated interferon and ribavirin in patients with hepatitis C virus genotype 1b in high viral loads. *Intervirology.* 2009;52(1):43-8.
5. Harrison SA, Rossaro L, Hu KQ, Patel K, Tillmann H, Dhaliwal S, et al. Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology.* 2010;52(3):864-74.
6. Foster T, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. *Am J Gastroenterol.* 2011;106(1):71-7.
7. Kostapanos MS, Milionis HJ, Elisaf MS. Rosuvastatin-associated adverse effects and drug-drug interactions in the clinical setting of dyslipidemia. *Am J Cardiovasc Drugs.* 2010;10(1):11-28.
8. Navarro JM, Escobar AG, Cabrera VEG. Could statins be a real therapeutic option for hepatitis C? *Hepat Mon.* 2011;11(7): 562-3.
9. Malaguarnera M, Giugno I, Ruello P, Pistone G, Restuccia S, Trovato BA. Effect of interferon on blood lipids. *Clin Drug Investig.* 1996;11(1):43-8.
10. Madhoun MF, Bader T. Statins improve ALT values in chronic hepatitis C patients with abnormal values. *Dig Dis Sci.* 2010;55(3):870-1.
11. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Restuccia N, Trovato BA. Efficacy of different schedules in the management of chronic hepatitis C with interferon-alpha. *Ann Med.* 1998;30(2):213-7.
12. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Ferlito L, Rampello L. Interferon alpha-induced depression in chronic hepatitis C patients: comparison between different types of interferon alpha. *Neuropsychobiology.* 1998;37(2):93-7.