



Are statins a remedy for all seasons?

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The hepatitis C virus (HCV) is a major cause of chronic liver disease, infecting ~185,000,000 persons, i.e. ~2.8% of the world population, and causing 350,000 deaths annually [1]. Chronic hepatitis C relentlessly leads to increasing degrees of fibrosis and ultimately cirrhosis. The fibrosis progression rate is variable, with some patients progressing to cirrhosis within a few years, while others may never progress even after decades from infection, depending on the presence and type of host, viral and environmental factors [2]. Although many of these factors cannot be modified [2], the fibrosis progression of hepatitis C can be effectively stopped with potent antivirals, leading to HCV eradication [3]. On the other hand, modification of the natural history of hepatitis C, by modulating the fibrogenic process, independently of any intervention on HCV, has so far been a chimera, despite intense preclinical research efforts. More in general, the clinical development of antifibrotics has been lagging behind, and no effective drugs have been validated in the clinical setting [4].

Statins may have some antifibrotic activity in pulmonary [5] and cardiac [6] fibrosis, although the mechanisms of these purported beneficial effects are undefined. Furthermore, there is some limited evidence on the antifibrotic effect of statins in experimental rat models of liver fibrosis [7,8], while clinical trials in patients with non-alcoholic fatty liver disease have been discouraging [9].

Simon *et al.* [10] analysed the association between statin use and liver fibrosis progression in a well-characterized cohort of chronic hepatitis C patients enrolled in the HALT-C trial [11]. All patients had advanced liver fibrosis (Ishak fibrosis score ≥ 3) at entry as well as a history of virological non-response to standard interferon therapies. After 24 weeks of retreatment with peginterferon alfa-2a and ribavirin, patients were randomized

based on their virological response at week 20: those with detectable serum HCV RNA were assigned for the next 3.5 years to either a maintenance therapy with 90 μg of peginterferon alfa-2a weekly without ribavirin or to an untreated control group. One of the goals of this trial was to evaluate whether a low dose of interferon-alpha maintenance therapy could improve histological outcomes independently of antiviral effects [11], by centrally assessing serial liver biopsies performed at enrolment and 1.5 and 3.5 years after randomization. In the study by Simon *et al.* [10], the use of statins was ascertained as part of a comprehensive medical history, obtained at enrolment and in the course of the study. Thus, a total of 543 patients with serial liver biopsies could be evaluated: 29 had received continuous statin therapy throughout the study, while 514 did not, thus serving as controls. Liver fibrosis progression occurred in 3 of 29 (10%) statin users and in 145 of 514 (29%) non-users. The hazard ratio for fibrosis progression among statin users compared to non-users was 0.31 (95% CI 0.10–0.97), after adjustment for a few of the known predictors of progression, such as body mass index, platelets and hepatic steatosis. In addition, the average change in the Ishak fibrosis score across the whole study period was -0.34 (SE 0.18) for statin users compared to $+0.42$ (SE 0.07) for non-users. Histological activity score or alanine aminotransferase level changes were not statistically different between statin users and non-users. The authors concluded that statin use is associated with a reduced risk of the liver fibrosis progression rate in chronic hepatitis C patients with advanced fibrosis, and that this beneficial effect does not appear to be mediated by a decrease in the level of liver inflammation.

Statins are extensively used in clinical practice for both primary and secondary prevention of cardiovascular events in patients with coronary artery diseases, diabetes mellitus and other atherosclerotic disorders. Statins exert their effect primarily via inhibition of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase, a transmembrane protein catalyzing a rate-limiting step in the mevalonate pathway that leads to the synthesis of isoprenoids and sterols. The major and best known effect of this inhibitory action is the reduction of circulating cholesterol. However, many beneficial effects of statins seem independent of cholesterol level reduction. These pleiotropic effects of statins include anti-inflammatory, immunomodulatory, antibacterial,

Keywords: Hepatitis C virus; Statins; Liver fibrosis; Hepatocellular carcinoma.

Received 4 September 2014; accepted 12 September 2014

* DOI of original article: <http://dx.doi.org/10.1016/j.jhep.2014.08.013>.

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Abbreviations: HCV, hepatitis C virus; HALT-C, hepatitis C antiviral long-term treatment against cirrhosis; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; SmgGDS, small GTP-binding protein GDP dissociation simulator.



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antiproliferative, antioxidant effects as well as the improvement of endothelial function and the suppression of platelet aggregation (reviewed in [12]).

On one hand, pleiotropic effects of statins are still secondary to the blockade of the mevalonate synthesis. This leads in fact to an impaired production of lipophilic prenyl compounds, involved in the post-translational modification of several factors, such as some small GTP-binding proteins (e.g. Rho, Rac, and Ras) and other proteins, whose localization to cell membranes depends on their isoprenylation [6,12]. In addition, impaired sterol synthesis may alter the composition of rafts, thus interfering with cell signalling and apoptosis, which may account, in part, for their antitumour effects [13]. Indeed, statins have been shown to reduce cancer-related mortality in several studies, including the vast survey on the Danish Civil Registration System database [14], and also to reduce the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C [15] or chronic hepatitis B [16]. On the other hand, also mevalonate-independent mechanisms seem to be involved. For example, a recent, interesting study showed that statins increased small GTP-binding protein GDP dissociation simulator (SmgGDS) in cultured human endothelial cells [17]. Adding prenyl compounds failed to counteract the SmgGDS increase. This effect explained the statin-associated protection against angiotensin II-induced medial thickening of coronary arteries and fibrosis in a mouse model [17]. SmgGDS favours degradation of the intracellular factor Rac1, thus blocking its induction of reactive oxygen species and providing a mechanism whereby statins may reduce oxidative stress [6], an interesting observation that may in part explain the antifibrotic effect of statins. Concerning the latter, Simon *et al.* [10] discuss some potential, additional mechanisms, such as activation of the Kruppel-like factor 2 in endothelial cells, which may lead to an enhanced transcription of vasoprotective genes, but clearly the fine details linking statins and fibrogenesis warrant further work.

The study of Simon *et al.* [10], although intriguing, has limitations as duly acknowledged by the authors. First, the low number of outcomes among statin users (3 out of 29) limited the ability to test for all potential confounders and the scope of the multivariable analysis that was conducted. Thus, these results should be considered as preliminary, and warrant a validation in additional studies with larger sample sizes and a greater number of outcomes. Second, the HALT-C trial included only patients with advanced liver fibrosis and in whom interferon was not contraindicated, i.e. a very selected population. More data is warranted in patients with milder fibrosis stages. Third, no dose effect could be assessed since the dose of statins used by study participants – a crucial parameter to assess a causal link with a clinical outcome – was not recorded. In addition, statins may have exerted their protective effect indirectly, i.e. via the suppression of HCV replication. Indeed, statins exert some degree of antiviral effect on HCV both *in vitro* and *in vivo*, especially when added to standard doses of interferon- α and ribavirin [18]. However, when the authors analysed the change in viral load over the study period, the median decline in HCV RNA was comparable among statin users and non-users, even after adjustment for randomization to the treatment or observation group. This suggests that the low dose interferon used in HALT-C was probably insufficient to produce any meaningful antiviral effect, and that therefore the reduction of HCV replication could not be a confounder in their study.

Another caveat that should caution against a wider use of statins consists of the fact that any purported beneficial effect should

be carefully weighed against the potential side effects of a long term statin use. Although the reported cases of significant hepatotoxicity are rare [19], statins, particularly the lipophilic ones (simvastatin, lovastatin and the blockbuster atorvastatin), still present some safety concerns, such as the risk of myopathies, renal dysfunction, cognitive and behavioural dysfunction (including memory loss), and – possibly – the development of diabetes mellitus [20]. In addition, drug-drug interactions may limit their use in patients with several comorbidities [20].

Thus, as usual, a word of caution is mandatory before we draw firm conclusions. For a hepatologist's point of view, statins may well reduce the degree of portal hypertension [21] and the risk of HCC in cirrhotic patients [15,16], but for these indications and as antifibrotic agents we need more data. Nevertheless, the paper by Simon and collaborators has the great merit of providing the basis for prospective cohort validation studies and intriguing working hypotheses that may (or may not) make statins, already among the top selling drugs of all times, a true remedy for all seasons, given their numerous beneficial effects in several fields of medicine other than hepatology.

Conflict of interest

FN is consultant for Roche and MSD, is advising Gilead, Janssen, Novartis, Bristol-Myers Squibb and Boehringer Ingelheim, and has received unrestricted research grants from Roche, Gilead and Novartis.

Acknowledgments

I wish to thank Drs Sophie Clément, Emiliano Giostra, and Nicolas Goossens for critically reading the manuscript.

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