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Statin, Beyond Hyperlipidemia toward a Novel Agent for Hepatitis C

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Dear Editor,

We read with great interest the article by Malaguarnera *et al.* (1) in this issue of Hepatitis monthly, in which the safety and efficacy of rosuvastatin plus interferon and ribavirin were evaluated in a randomized controlled trial. Sustained viral response was observed in 40% of the standard-care group and 51% of the triple-therapy group, and this was associated with improvement of steatosis and fibrosis without causing side effects. Despite the importance of this study, we think that the clinical implications extracted from this study deserve further evaluation. In particular, we question some components of the study design.

First, the authors did not clarify how they calculated the sample size of this study. Because the sample size is so small, it may be underpowered. All of the results, however, are around borderline significance, and we suspect that a larger study would have shown quite a different pattern of results. Second, it is not clear why the authors chose to use conventional interferon instead of the golden standard that is available, pegylated interferon. Third, it is not clear if all patients had steatosis at baseline or if the degree of steatosis varied between the study groups (2.3 ± 0.4 *vs.* 1.9 ± 0.3).

Some studies have suggested that the interleukin 28b polymorphism pattern is associated with a changing pattern of lipid metabolism in hepatitis C (2). Patients carrying genotype CC of the SNP rs12979860 exhibited a higher rate of sustained viral response with higher levels of total cholesterol and LDL-cholesterol. However, the interaction of lipids-IL28b was not seen in noninfected people. Thus, we need to keep in mind that the association between statins use and improved sustained viral response could be biased. Patients with the favorable genotype showed higher levels of cholesterol, and they received statins and achieved a sustained response, but the main reason might not be statins use but the IL-28b polymorphism pattern.

In view of the suboptimal response to the current antiviral treatments, it is imperative that thought be given to explore novel therapies. Targeting host factors is a potentially novel approach that could improve response rates to treatment (3). Overall, the current study provided evidence on the potential value of the use of statins in cases of chronic hepatitis C, especially for the group of patients who already needed statins (i.e. patients with hypercholesterolemia and diabetic patients). Data from several recent studies using statins in combination with Peg-IFNα/RBV are provocative (4-10). Moreover, the ways in which statins work include reducing serum lipids and up-regulation of the low-density lipoprotein receptors

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(LDL-R). Hepatocytes acquire cholesterol via endocytosis involving LDL-R. The most important ligands for this receptor are LDLs, which are responsible for the transport of the majority of plasma cholesterol (11). LDL-R is one of the postulated receptors in HCV entry (12). Despite the potential value of the use of statins in chronic hepatitis C patients, especially for patients who already need statins (i.e., patients with hypercholesterolemia and diabetic patients), the use of statins raises many questions. First, the effects of statins on HCV viral load have been relatively modest, short lived, and not even confirmed in all studies. Second, this varying response suggests that many variables are likely involved, including both host and viral factors that alter responses to antiviral therapy, even when statins inhibit HCV replication. Because statins reduce serum lipids and up-regulate LDL-Rs, they may be associated with increased HCV viral entry. However, in view of the emerging data of the antiviral properties of statins, more studies are needed to clarify this issue. Additionally, the function of LDL-Rs in HCV infection remains controversial because the role of this receptor in the in vitro HCVcc infection model has yet to be demonstrated (13). However, we cannot exclude the possibility that LDL-Rs mediate an alternative pathway of HCV cell entry. Tiedemann *et al.* recently hypothesized that statins may have a multifactorial effect on chronic HCV infection. These compounds interfere with HCV replication by induction of the enzyme heme oxygenase 1 (HO^{-1}) and subsequent reduction of cellular levels of reactive oxygen species (14). This effect is associated with induction of endogenous antiviral defense mechanisms by induced expression of IFN alpha 2 and 17 and target genes of IFN signaling (i.e., OAS 1 and 2, PKR, and HRI). Finally, the safety concerns potentially associated with the use of statins cannot be ignored (15).

In conclusion, Malaguarnera *et al.'s* (1) study will certainly broaden our horizons with respect to the treatment of chronic HCV. However, we have written to share our concerns about the study design, and we hope to stimulate a scientific discussion with the authors.

Author's Reply: Statin, Beyond Hyperlipidemia toward a Novel Agent for Hepatitis C

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Dear Editor,

We sincerely appreciate our colleagues Khattab *et al.* taking time to provide comments and feedback by about our recent article, "Statin, Beyond Hyperlipidemia Toward a Novel Agent for Hepatitis C" (1). It is important to mention that this was a pilot study. Pilot studies are frequently carried out before large-scale quantitative research in an attempt to avoid time and money being wasted on an inadequately designed project. A pilot study is usually carried out on members of the relevant population but not necessarily on those who will form part of the final sample. This is because it may influence the later behavior of research subjects if they have already been involved in the research. A pilot experiment

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is often used to test the design of the full-scale experiment, which then can be adjusted as needed to improve the chances of a clear outcome.

The short circulating half-life of unmodified IFN-alpha makes frequent dosing (daily or 3 times weekly) over an extended period (6 to 12 months or more) necessary versus pegylated interferon. The PEG (polyethylene glycol) protects the molecule from proteolytic breakdown and increases the biological half-life of the interferon protein, which is 20 to 60 hours. Regardless, several studies have found no differences in the efficacy of the lower-dose peginterferon and interferon (16). Additionally, symptoms such as myopathy or rhabdomyolysis, varying from mild to severe, occurred in some patients. To verify these kinds of situations, it is important to have a drug with a short half-life. The resolution of signs and symptoms of rhabdomyolysis upon withholding therapy particularly suggests dose dependence of the phenomenon as well as the feasibility of continued therapy with close follow-up after dose modification. This phenomenon can verify when IFN therapy is associated to ribavirin and statins. For this reason we chose IFN rather than PegIFN as the gold standard of therapy.

The association between hepatic steatosis and HCV is well established in the literature. Moreover, steatosis is considered to contribute greatly to the progression of liver fibrosis by modulating host-cell lipid metabolism (17). Suspected underlying molecular mechanisms include interactions between HCV proteins and intracellular lipid metabolic pathways. Recent studies have suggested that the nucleocapsid of HCV (core) acts as a pathogenic factor involved in lipid droplet accumulation, changes in lipogenic gene expression, and the activity of lipogenic proteins in a genotype-specific manner. Liver steatosis is frequently observed in HCV infection, and HCV is often implicated in the pathogenesis of steatosis. In particular, the progression of steatosis depends on several host-related cofactors, such as age, gender, alcohol consumption, overweight, insulin resistance, and coinfections (18). Although these factors may occur independently of HCV, a direct role of HCV infection in their pathogenesis has been reported. Whereas the virus-induced steatosis does not seem to have major clinical consequences, the so-called "metabolic" steatosis and underlying insulin resistance may not only modify the clinical and histological course of chronic hepatitis C, but also may influence the response to interferon alpha-based therapy (19). Some studies have suggested that interleukin 28B plays a role in the treatment-response differences among patients with chronic hepatitis C undergoing interferon therapy. Interferon λ induces antiviral, antiproliferative, and immune responses. IL28B, located on chromosome 19, encodes interferon λ 3 and has been reported to be involved in the suppression of HCV replication (20).

The life cycle of HCV is intimately linked to the lipid metabolism of the host. In particular, HCV exploits the metabolic machinery of the lipoproteins in several steps of its life cycle, such as circulation in the bloodstream, cell attachment and entry, assembly, and release of viral particles. However, the details of how HCV interacts with and influences the metabolism of the host lipoproteins are not well understood. This point suggests that lipid-lowering medications might have antiviral properties in vivo. In particular, this indicates apoA-I as a new possible target for antiviral therapy (21).

Another point is the anti-inflammatory and antiapoptotic heme-degrading enzyme heme oxygenase-1 (HO-1) has been shown recently to interfere with the replication of HCV. Although the precise mechanisms underlying hepatocellular injury associated with HCV have yet to be determined, there is compelling evidence that HCV produces increased oxidative stress in human liver cells that is linked to the production of reactive oxygen species (22) and consequent increases in cellular lipid peroxidation and other oxidative damage. Oxidative stress appears to be an important aspect of HCV-induced hepatocellular injury. Microsomal heme oxygenase-1 (HMOX-1) is an inducible cytoprotective enzyme that catalyzes the initial and rate-limiting reaction in heme catabolism to release free iron and equimolar amounts of carbon monoxide and biliverdin (22). A study by Lehmann (23) demonstrated that the antioxidant biliverdin reduced HCV replication in vitro by triggering the antiviral interferon response. Therefore, drugs with antioxidant and immunomodulatory effects might contribute to hepatoprotective activity.

Investigations of the oxidant–antioxidant system of HCV-expressing cells can provide important clues to better understand the pathobiology of the virus and help formulate new strategies to treat it (24).

We conclude that the treatment decisions for patients with HCV infection require drugs that enable a good quality of life and minimize side effects at full dosage. Moreover it is important to look for new strategies that interfere with the virus's metabolism and against the infection too.

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