

Novel Biomarkers Associated With the Outcome of Interferon-Based Hepatitis C Virus Therapy



The past 25 years since the discovery of hepatitis C virus (HCV) have been marked by significant advances in both understanding the biology of the virus and its interactions with the human host as well as developing treatment strategies that now allow a majority of patients to be cured. Combination therapy consisting of pegylated interferon- α (IFN α) 2a/2b and ribavirin was the standard of care for treating hepatitis C for almost a decade until the approval of first generation NS3/4A protease inhibitors in 2011.¹ A variety of host factors that influence the outcome of IFN-based treatment regimens have been identified and established as predictors for the achievement of a sustained virological response (SVR). The best-characterized host factors are single-nucleotide polymorphisms within the interleukin 28B (IL28B) gene locus that are associated with an approximately twofold change in treatment response.² Other patient characteristics that influence treatment outcome, such as insulin resistance, hepatic steatosis, liver fibrosis, and patient age, have been described, but their role as a predictor for SVR is less well characterized.³

In the search for biochemical markers that can predict the outcome of IFN-based therapies, several studies identified baseline low-density lipoprotein (LDL) levels to positively correlate with SVR rates.^{4,5} The knowledge that the HCV life cycle is closely tied to the hepatic lipid pathway has resulted in the identification of several potential treatment targets, but the link between HCV replication and LDL in particular was not obvious.⁶

Based on their previous observation that oxidized LDL (oxLDL) acts as an HCV entry inhibitor by disrupting the interaction between HCV and one of its entry factors, scavenger receptor class B member 1 (SR-BI), Solbach et al⁷ analyzed the oxLDL levels of 379 patients from the INDIV-2 study chronically infected with HCV genotype 1. The authors demonstrated that oxLDL serum baseline levels were an independent predictor of SVR in IFN-based treatment regimens. Area under the receiver operating characteristic curve values of oxLDL and LDL were not statistically significantly different, so both parameters are largely equivalent predictors of SVR, adding to the appeal of these findings in a clinical setting because LDL is a routine parameter unlike oxLDL.

As a next step, Solbach et al addressed how the correlation between oxLDL and SVR could be explained. They hypothesized that (1) elevated oxLDL levels may result from an ongoing inflammatory, antiviral immune response, (2) oxLDL might enhance the antiviral effect of exogenous IFN, or (3) oxLDL may reduce the infection of new hepatocytes during IFN treatment, thereby enhancing the clearance of infected cells.

They were able to rule out their first hypothesis, as there was no correlation between oxLDL and serum alanine aminotransferase or serum ferritin levels, markers of hepatic inflammation and systemic inflammation, respectively. To test their second hypothesis, Solbach et al measured HCV replication in vitro as a function of pegylated IFN concentration in the presence or absence of oxLDL using genotype 1b and 2a subgenomic replicons and cell culture-produced HCV. As they did not observe a significant difference between the two tested conditions, they concluded that oxLDL does not alter IFN sensitivity in their experimental system.

Finally, the authors found that oxLDL-treated cells, but not LDL-treated cells, showed a significant inhibition in the spread of HCV to adjacent cells compared with untreated control cells. Interestingly, when reanalyzing the data of their patient cohort, they observed a modest but significant correlation between oxLDL serum levels and the rate of infected cell loss, which is thought to be an important predictor for treatment outcome.

Clinicians, especially in resource-limited environments, may take oxLDL or LDL serum levels into consideration for treatment decisions although these predictors are unlikely to broadly affect such decisions in real-world settings. The significance of this study lies more in adding to our understanding the pathophysiology of HCV. The authors' data indicate that oxLDL is likely not only the molecule responsible for the previously observed positive correlation between LDL serum levels and SVR in IFN-based treatment regimens, but also that this effect is possibly due to an oxLDL-mediated inhibition of HCV cell-to-cell spread. Taken together with their previous observation that oxLDL interferes with the interaction of HCV and its entry factor SR-BI, the authors provide additional evidence that SR-BI may be needed for the cell-to-cell spread of HCV, which could have implications for the further development of HCV entry inhibitors.

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Conflicts of interest

The authors disclose no conflicts.

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