Reply to: “Lower incidence of hepatocellular carcinoma in patients with transient virologic response to peginterferon and ribavirin combination therapy: Is it really the effect of the therapy?”

To the Editor:

We appreciate the interest shown in our study by Toyoda et al. and thank them for their comments [1]. Due to space limitations, we were unable to report extensive details of viral and host factors, including hepatitis C virus (HCV) core protein and interleukin 28B (IL28B) genotype. We fully agree that the amino acid (aa) substitutions at position 70 in the HCV core region are associated with poor virological response to pegylated interferon α (PegIFN-α) and ribavirin (RBV) treatment, hepatic steatosis, insulin resistance, and development of hepatocellular carcinoma (HCC). We also previously reported that the diversity of the HCV core region is significantly correlated with abnormal alanine aminotransferase (ALT) levels [2]. Unfortunately, we do not have information on the HCV core antigen sequence of the studied patients because this was a multicenter study that was started before publication of the findings of oncogenic potential by treatment-resistant substitution of core aa 70 (glutamine/histidine) [3]. Although substitutions in the core region might affect the development of HCC, analysis of a fixed condition such as this is difficult because the sequence of the core region sometimes changes with time [4] or during antiviral treatment [5]. Recently, deep sequencing has become available for the determination of viral genetic variations. According to this technology, treatment-resistant substitution of core aa 70 was found to be contained in most cases, even when not detected by direct sequencing. The structural and functional alterations of core protein and the relation to the occurrence of HCC need to be further studied.

We reported that the incidence rate of HCC for patients with IL28B TT (rs8099917) genotype after antiviral treatment was significantly lower than that for patients with non-TT genotype, as Toyoda et al. reported [6]. However, there was no significant difference in the incidence rate of HCC in patients who had not received antiviral treatment between the IL28B TT and non-TT genotypes [4], despite the fact that the IL28B non-TT genotype was related to treatment-resistant substitution of core aa 70. Therefore, further studies are needed to determine the mechanisms related to HCV core aa 70, IL28B genotype, and the development of HCC.

We concluded that transient virological response (TVR) was associated with a lower risk of development of HCC in comparison with the non-virological response (NVR) in a prospective study and emphasized that this association was observed not only for cirrhotic patients, but also for non-cirrhotic patients aged 60 years and over. We did not merely suggest that TVR was directly reducing HCC development. In our discussion, we stated the possibility of the efficacy of viral suppression compared with previous studies. In addition, TVR patients have sometimes redounded to benign clinical outcomes. For instance, our study showed that the percentage of TVR patients who developed hepatocarcinogenesis following eradication of HCV RNA by antiviral therapy was significantly lower than that of NVR (36.2% vs. 17.1%, p < 0.001). BR in non-sustained virological response (non-SVR) patients has been reported to contribute to the inhibition of the development of HCC [8]. In fact, our study showed that the HCC incidence rate of BR/TRV was significantly lower than that of non-BR/TRV patients (0.9% vs. 6.2%, p < 0.05). We previously reported that the liver stiffness measurements by transient elastography (FibroScan®) of BR/non-SVR patients was significantly lower than that of non-BR/TRV patients (2134–2141). We reported [6]. However, there was no significant difference in the incidence rate of HCC in patients who had not received antiviral treatment between the IL28B TT and non-TT genotypes [4], despite the fact that the IL28B non-TT genotype was related to treatment-resistant substitution of core aa 70. Therefore, further studies are needed to determine the mechanisms related to HCV core aa 70, IL28B genotype, and the development of HCC.

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patients decreased continuously for two years after the end of treatment [9]. Therefore, an additional effect of TVR may be that it leads to lower risk of the development of HCC.

In summary, our study confirmed a lower incidence of HCC in patients with TVR compared to those with NVR, probably because TVR was associated with benign clinical outcomes.

We thank the Journal of Hepatology for providing the opportunity for us to engage in this interesting discussion.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


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Understanding triphasic HCV decline during treatment in the era of IL28B polymorphisms and direct acting antiviral agents via mathematical modeling

To the Editor:

Howell and colleagues [1] have recently provided important insights into the relationship among viral kinetic patterns, including the triphasic pattern (Fig. 1 in [1]), ethnicity (African Americans, AA, and Caucasian Americans, CA) and IL28B genotypes (rs12979860; CC, TC and TT genotypes) during pegylated interferon-alpha-2a (PegIFNα-2a) + ribavirin (RBV) treatment. Their study strongly suggested differences in viral kinetic patterns under PegIFNα-2a ± RBV between AA and CA are associated with IL28B genotypes and elegantly showed that the difference disappears in AA or CA subjects with the same favorable allele (CC). Interestingly, Howell et al. described subjects in whom a static or increasing viral phase (termed here a shoulder) was observed during days 2–7 after treatment initiation (Fig. 1 in [1]). While the nature of the shoulder phase is still not known, Howell et al. [1] related this phase to “a delay in the pharmacologic activity of ribavirin” or “lower PegIFNα-2a effectiveness”. We sought here to clarify the current theory behind the nature of the shoulder phase and provide further insights into the subject.

A transient viral decline was observed in some HCV-monoinfected subjects during the first week of RBV monotherapy [2]. In a recent study, in which subjects were treated with RBV alone for 4 weeks, there was no association between HCV RNA kinetics measured weekly and IL28B genotypes (submitted). In HIV/HCV co-infected subjects treated with PegIFNα-2b and RBV, median RBV area under the curve levels were lower in sustained viral responders (SVRs) compared with non-SVRs at days 3 and 7 and were associated with a continued viral decline during days 3–7 (in SVRs) compared to a shoulder in non-SVRs (Fig. 2C in [3]). Unfortunately, data on IL28B genotypes is not yet available to be linked to our previous studies [2,3], but if indeed subjects with IL28B CC genotypes in Howell et al. are associated with early lower RBV levels and/or transient viral decline during the first week, then it could, partly, explain their findings.

A more evident cause of the viral shoulder phase is the known pharmacokinetics of PegIFNα which peaks and then declines during the first week of treatment [4,5]. To explain the shoulder phase with the standard model [6], the PegIFNα concentration in serum, C(t), was coupled with its effectiveness, ε(t), in blocking viral production/release [4,5] (see Fig. 1 for equations and parameters definition). Using this theory, the observed viral kinetic patterns from Howell et al. can be predicted (Fig. 1). Interestingly, we recently showed, in HIV/HCV (genotype 1/3) co-infected subjects...