Letters to the Editor

References


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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:

Ogawa et al. reported interesting and important findings, based on a large prospective cohort, regarding the effect of combination therapy with peginterferon and ribavirin on the incidence of hepatocellular carcinoma (HCC) [1]. They reported lower incidence of HCC after treatment in patients with transient virological response (TVR, defined as relapse or breakthrough) as well as in patients with sustained virological response (SVR), relative to patients with non-virological response (NVR). The suppressive effect of this antiviral therapy on the development of HCC in patients with SVR has been established by several reports and can be explained by the eradication of hepatitis C virus (HCV), resulting in the release of inflammation and improvement of liver fibrosis [2]. However, it is unclear why the incidence of HCC after treatment was also lower in patients with TVR than in those with NVR, despite the presence of viremia after treatment. Ogawa et al. attributed this observation to the preventive effect of complete HCV suppression during therapy on the development of HCC.

Previously reported viral and host factors that are strongly associated with response to antiviral therapy with peginterferon and ribavirin [3,4] may also be associated with the pathogenesis of HCC. Amino acid substitutions in the HCV core region, a viral factor reportedly associated with response to peginterferon and ribavirin therapy in patients with HCV genotype 1b [3] (i.e., the vast majority of subjects in the study by Ogawa et al.), are also associated with the development of HCC [5]. Regarding host factors associated with the response to combination therapy [4], genetic polymorphisms near the IL28B gene are reportedly associated with hepatic steatosis [6] and interact with amino acid substitutions in the HCV core region [5,7]. Both hepatic steatosis and amino acid substitutions in the HCV core region are associated with the development of HCC [5,8]. In addition, amino acid substitutions in the HCV core region are reportedly associated with the development of HCC, even in patients who achieved SVR [9]. Ogawa et al. reported, without providing detailed data, a higher incidence of HCC in patients bearing the non-TT genotype of rs8099917 near the IL28B gene, which is unfavorable to response to the combination therapy; this observation is also consistent with our previous report [10].

These results suggest that differences in HCC incidence based on the outcome of antiviral combination therapy are mainly attributable to these viral and host factors. It is possible that Ogawa et al. simply classified patients based on the likelihood of developing HCC upon observing the response to the combination therapy (i.e., TVR and NVR). It would be interesting if the authors were to analyze the incidence of HCC in relation to the outcome of combination therapy based on these host and viral factors. In addition, it would be interesting to investigate genetic polymorphisms near the IL28B gene and amino acid substitutions at residue 70 of the HCV core region, in the 13 patients who developed HCC despite the achievement of SVR.

Given the existence of factors associated with both therapeutic response and incidence of HCC, one should be cautious in drawing the conclusion that lower incidence of HCC in patients with TVR, relative to those with NVR, actually reflects the “suppressive effect” of peginterferon and ribavirin combination therapy on hepatocarcinogenesis.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.
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 hepatic decompensation was lower than that of NVR patients, and Morgan et al. showed similar findings to our study [7]. Moreover, the rate of biochemical response (BR; ALT <30 IU/L at six months after the antiviral treatment) of TVR was significantly higher 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/TVR was significantly lower than that of non-BR/TVR patients (6.2% vs. 17.1%, p <0.05). We previously reported that the liver stiffness measurement by transient elastography (FibroScan®) of BR/non-SVR

References


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