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LETTER TO THE EDITOR

Oversimplification of the link between hepatitis C treatment and hepatocellular carcinogenesis?☆,☆☆

¿Sobresimplificación de la conexión entre el tratamiento de la hepatitis C y la carcinogénesis hepatocelular?

I read with interest the case report presented by Tapia-Sosa et al.[1] The authors' contribution has undoubtedly benefited the global discussion regarding the correlations between direct-acting antiviral therapy (DAA) in the treatment of chronic hepatitis C (HCV) infection, and the disease course of hepatocellular carcinoma (HCC). However, the authors may have risked oversimplifying the link between DAA therapy and HCC pathogenesis by raising the possibility of a causal relationship. Although the 2 patients in the paper presented with cirrhosis pursuant to HCV infection, this only serves to strengthen the argument that irreversible changes might have been induced by HCV in the cellular architecture in the liver. Hence, although HCV is eradicated through DAA, such changes remain and influence the disease course of HCC.

Chronic HCV infection is capable of eliciting various epigenetic changes to hepatocytes during the course of infection. According to recent studies,[2,3] chronic HCV infection is conducive to epigenetic modifications to histone H3, a DNA packaging protein. The epigenetic change, H3K27ac, which involves the acetylation of the lysine residue at N-terminal position 27 of the protein, is found to be associated with an increase in HCC risk, where there is altered expression of the genes associated with HCC pathogenesis. Eight genetic signatures are identified (WNT10A, JUNB, FOSL2, MYCN, TNFAIP3, KLF4, EDN1, and PCSK9). Moreover, such epigenetic modifications persist after HCV cure through DAA therapy. The fact that these changes precede hepatocellular carcinogenesis strengthens the argument. H3K27ac is also associated with greater risk of hepatic fibrosis, which is a major risk factor of HCC progression.[4]

Secondly, I would recommend that the authors provide a more comprehensive picture of the patients they presented, since nuances in the medical history can suggest alternative explanations towards the observed development of HCC after the administration of DAA therapy. It is uncertain whether the two patients had any concurrent etiologies for hepatocellular carcinogenesis. For instance, if a patient were co-infected by HCV and chronic hepatitis B (HBV), the implementation of DAA therapy would lead to the eradication of HCV, but also a simultaneous increase in HBV disease activity afterwards. This increase can be associated with *de novo* hepatocellular carcinogenesis or cancer progression. In this case, being cognizant of the time interval between the attainment of sustained virologic response (SVR) and hepatocellular carcinogenesis is key.

Thirdly, such results have to be interpreted in light of the socio-epidemiological landscape in Mexico. Since the proportion of people who inject drugs is relatively high in the region, coupled with the risk of viral transmission via blood transfusion, the two patients reported may have experienced human immunodeficiency virus (HIV) co-infection, which carries a substantially higher risk of HCV recurrence than that in patients who are mono-infected with HCV (summary 5-year risk: 15.02%; 95% CI: 0.00-48.26%, versus 0.95%; 95% CI: 0.35-1.69%).[5] There is also a risk of *de novo* contraction of hepatitis C through established transmission routes, as mentioned above. This is particularly relevant if the patient has a continuing history of injection drug use and coagulopathies that require regular blood transfusions.

Ethical considerations

Informed consent from patients is not required. This manuscript is a response to a published article and requires no approval from an ethics committee. The author also declares that this article does not contain personal information that enables patient identification.

Financial disclosure

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Conflict of interest

The author declares that there is no conflict of interest.

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Reply to Alexander Ng. Response to Letter to the Editor☆

Respuesta a Alexander Ng. Réplica a la Carta al Editor

We wish to thank Dr. Ng for his interest in our case report of two patients that developed hepatocellular carcinoma (HCC), following therapy with direct-acting antivirals (DAAs). As a case report, we did not intend to establish causality[1]. As we discussed in our article, we agree that there appears to be no link between DAA therapy and *de novo* or recurrent HCC. This is supported by a recent meta-analysis: Ma et al.[2] evaluated the incidence of HCC in 276,848 hepatitis C virus (HCV)-infected patients treated with IFN or DAA-based therapy. They found that treatment with either agent reduces the risk of developing HCC in patients with chronic HCV.

HCV causes the cell to develop adaptative mechanisms to stress that facilitate carcinogenesis. Exosomes contain miRs that are involved in viral replication and carcinogenesis. HCV-infected liver cells produce high levels of miR-122. Treatment with DAAs causes a decrease in miR-122 and its loss is associated with HCC[3]. HCV also causes derangements in the immune response. The liver contains a high number of mucosal-associated invariant T (MAIT) cells. HCV upregulates immune activation markers, such as HLA-DR, CD69, and PD-1, which leads to chronic immune activation of those cells and immune exhaustion. DAAs decrease the levels of IL-18, one of the cytokines that stimulates MAIT cells, causing a decrease in intrahepatic inflammation and cytotoxicity. However, even after a virologic cure, MAIT cells continue to be dysfunctional. Other studies showed that memory CD8 T cells produced less IFN-γ and TNF-α following antigen challenge, in patients with HCV. Like MAIT cells, CD8 T cells maintain an exhausted phenotype after cure. Moreover, intrahepatic regulatory CD4 T and T-reg cells are expanded in the blood and liver of patients with chronic HCV and remain unchanged after DAA therapy[4]. These findings suggest that HCV causes epigenetic and immunologic changes, independent of DAA-induced cure, that predispose patients to HCC.

We agree that a more detailed past medical history could have been helpful for the reader. Our patients' past medical history was negative for drug use, high-risk sexual activities, and diseases needing blood transfusions. Following the most recent guidelines[5], both of our patients tested negative for hepatitis B virus (HBV) and HIV. Regarding the attainment of sustained virologic response (SVR) and the development of HCC, we diagnosed HCC recurrence before finishing DAA therapy in the first patient and *de novo* HCC 3 months after finishing treatment in the second patient. We consider that HCV was cured in both patients, as they had an SVR. We believe that the irreversible changes caused by HCV infection were responsible for the development of HCC in our patients.

Finally, most of the available evidence points toward an end to the controversy regarding the association between DAAs and the development of HCC.

Ethical considerations

Informed consent was obtained from both patients prior to publication. This manuscript does not contain any patient information that might enable their identification. The utilization of de-identified patient data for the original and related manuscripts was approved by the ethics committee of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*.

Author contributions

RTS and VMPZ were involved in chart reviewing. MSR, RTS, VMPZ, MDH and IGJ were involved in the planning, drafting, writing, and revision of this manuscript.

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