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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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Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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Determination of socioeconomic and cultural factors and regional etiologic variability in liver cirrhosis☆

Determinación de factores socioeconómicos y culturales y variabilidad etiológica regional de la cirrosis hepática

Dear Editors,

We recently reviewed the original article, ''Influence of socioeconomic and cultural factors in the etiology of cirrhosis of the liver'' by Roesch et al.[1]. We believe the author should have included the income levels of the population analyzed, given that they are strongly associated with the self-care variable and etiologic variability in Mexico.

Park and Shin evaluated the monthly income of their patients with liver disease, categorizing them into 4 groups, according to income, observing better self-care behavior in patients with higher income (≥3,000 won) (33.3%) and poorer self-care behavior in lower-income patients (<1,000 won) (5%)[2]. Self-care is highly influenced by information sources, such as those provided by healthcare personnel (80.8%), newspapers and magazines (11.6%), and the experiences of other patients with cirrhosis of the liver (7.5%)[2].

The analysis of the relation of economic factors to the etiology of liver cirrhosis in patients is a key element in all studies with an epidemiologic profile, as shown by Mukherjee et al. They conducted a study on a Hindu population that presented with severe forms of liver disease, including cirrhosis of the liver, and their association with poverty levels[3]. Hepatitis C virus (HCV) was the second most frequent etiologic agent in patients with the poorest economic status[3].

Data on the etiology of liver cirrhosis can show considerable local variability, as was observed in different regions of India. The most frequent viral cause (HCV) was found in the Northern regions, hepatitis B virus (HBV) in the Eastern and Southern regions, and the non-viral etiology (alcohol) was found in the Northeastern region[3]. Likewise, in the Colombian epidemiologic characterization of liver cirrhosis carried out by Escorcia Charris and Marrugo Balceiro, they reported the distribution in 7 departments, finding a majority of patients diagnosed with cirrhosis of the liver in the Atlántico department (70.4%), whereas the other departments accounted for only 29.6%[4]. Unfortunately, their study did not include an analysis of the etiologies that predominated in each department —information that would be very useful for national health strategies.

We believe that the factors in the present study should have been studied further, given that they greatly influence the etiology of cirrhosis of the liver and the increase in the number of cases; cultural and environmental factors modify its etiology, as well.

Ethical considerations

Informed consent was not required for the drafting of the present document, given that it was written based on studies that included informed consent before participating in the research.

We declare that our article does not require authorization by the Research Ethics Committee of the Universidad Privada

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