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OPINIONS

The Direct-Acting Antivirals for Hepatitis C Virus and the Risk for Hepatocellular Carcinoma

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ABSTRACT

The increase of incidences of Hepatocellular Carcinoma (HCC) will continue in the next decades. The therapies about hepatitis C infection has been questioned as a risk factor. Some authors emphasized that sustained virologic response (SVR) with interferon-based therapy reduced the risk of developing HCC. In contrast, some publications that to suggest an increasing risk of HCC in patients treated with Direct-Acting Antivirals (DAA). Whether these therapies are associated with an increased risk of HCC remains to be studied and continued long-term observational studies will be needed. The goal in HCV care needs to go beyond merely achieving an SVR.

Key words. Liver. Cancer. Drugs. Hepatitis.

Cirrhosis is the end stage of every chronic liver disease. The most common causes of hepatic fibrosis are the viral infection (hepatitis B and C). Furthermore obesity rates have increased the risk of liver injury through nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), as well as consumption of alcohol and autoimmune diseases. At the stage of liver cirrhosis, patients are at elevated risk of liver failure and hepatocellular carcinoma (HCC), two complications that shorten their life expectancy.

Interestingly, Davis, *et al*.[1] in 2003 conducted an elegant study projecting the complications of HCV in the United States. Those investigators predicted that, according to their model, the projected total number of patients with HCV to decline gradually over the next three decades (2020, 2030 and 2040). However, the number of cases with cirrhosis increased to 25% in 2010, 32% in 2020, 36% in 2030, and 38% in 2040. In the same way, the number of cases of HCC were projected to increase over the next 2 decades, nearly doubling before stabilizing. Our group[2] observed the projected trends in liver disease prevalence in Mexico from 2005 to 2050, and we predicted that the prevalence of chronic liver diseases will become high and HCC will continue increase over the time.

The treatments about this topic have been evaluated over the years, and today we have to be aware of the advantages and disadvantages of each of them. On the one hand interferon-based regimens with the combination of Pegylated interferon and ribavirin result in sustained virologic response (SVR) in approximately half of treated cases. Several studies have confirmed the benefits of this treatment by reducing the risk of HCC. Unfortunately, the achievement of SVR did not eliminate this risk. For example, Yamashita, *et al*.[3] reported that patients who had a SVR after the treatment with Pegylated interferon and ribavirin developed a HCC in 26% (the cumulative rates of HCC were 3.1, 10.1, and 15.9% at 5, 10, and 15 years, respectively). Similarly, Innes, *et al*.[4] identified individuals who achieved SVR with interferon-based antiviral therapy in Scotland between 1996-2011 using a national database, then followed them 5.2 years after SVR. The investigators calculated standardized mortality ratios to compare the frequency of mortality in SVR patients to the general population and reported a higher mortality rate (HR 1.9). The main causes (66%) of the death was

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due to drug-related causes and death from liver cancer. On the other hand, in a multicenter cohort study,[5] the researchers observed the low risk for all cause-mortality in patients with chronic hepatitis C who achieved SVR with interferon-based treatment. The risk was almost 4-fold lower compared without SVR. In Canada, Janjua, *et al.*[6] reported on a provincial British Columbia database of 8147 patient treated with interferon-based therapy and found that SVR was associated with a lower risk of HCC (subdistribution HR = 0.20, 95% CI: 0.13-0.3). They emphasized that SVR with interferon-based therapy reduced the risk but that a significant risk of HCC still remained.

Nowadays with the introduction of direct-acting antiviral (DAA) for the treatment of HCV the viral eradication in most if not all patients who undergo treatment. The question arise if those patients treated with the DAA have a lower risk to develop HCC than those patients treated with pegylated interferon and ribavirin. Interesting there are some publications that to suggest an increasing risk for HCC in patients treated with DAA.[7] But other publications did not support this finding.

From a treatment perspective, it appears that HCC itself diminishes the likelihood of virus eradication. In Prenner's study published recently,[8] the aim of that study was to assess the efficacy of all oral-DAA regimens in HCV + cirrhotic patients who have or had HCC compared to those without HCC. The investigators studied 421 patients HCV with cirrhosis of whom 33% had active, or a history of, HCC. The most frequent genotype was type 1 (86%) and 60% had been previously been treated for HCV. The results of this study showed that the presence of active HCC tumor at the time of HCV treatment initiation was associated with treatment failure using all-oral DAA regimen ($p = 0.04$) but that successfully treated HCC was associated with a high likelihood of achieving SVR.

In addition, some studies report surprisingly high rates of recurrence HCC in patients treated successfully with DAA regimens after their tumors had been treated, presumably successfully, by various therapies other than liver transplant. This suggests that DAA associated SVR does not protect against HCC recurrence post HCC treatment. For example Conti, *et al.*[9] confirmed in patients previously treated for HCC that there is still a high risk of tumor recurrence, despite successful DAA treatment. They analyzed 344 patients' cirrhotic patients, 285 without HCC and 59 with previous HCC with follow up for 24 weeks. The development of recurrent HCC was found in 17 patients of 59 (with previous HCC) compared to 9 of 285 without. Advanced cirrhosis represented a predictor of recurrent HCC.

At the same time Reig, *et al.*[10] observed HCC in patients with a complete response after HCC treatment by resection, ablation, or chemoembolization and after antiviral therapy using DAAs. The patients who achieved a SVR had an unexpectedly high rate of HCC recurrence (28%).

If the previously mentioned projections are accurate, we can expect increases in the complications of cirrhosis in the future. Therefore the long-term non-virologic effects of antiviral treatment must continue to be evaluated. Some authors hypothesize that the type of therapeutic option employed to treat the HCC may condition its reappearance and this may influence the apparent oncologic DAA failure (i.e. HCC recurrence). Although the early studies reporting HCC post-DAA may be due to an unforeseen selection or ascertainment bias, never-the-less, they are hypothesis-generating and underscore the fact that patients with cirrhosis who have achieved a SVR still need regular surveillance for HCC.

In conclusion, the risk for developing HCC remains, even though SVR has been achieved and these patients should undergo HCC monitoring for the long term. Whether DAAs themselves are associated with an increased risk of HCC remains to be studied and continued long-term observational studies will be needed.

The goal in HCV care needs to go beyond merely achieving an SVR. We should identify in all patients the risk factors for complications, comorbidity's and we have to know the hepatic damage at the time patients achieve SVR and in this way we can determine the frequency of the medical visits. In this regard, we agree with Jacobson, *et al.,*[11] who have published a clinical practice update proposing a modulation of surveillance or management of gastroesophageal varices, modification of the use or dosing of medications metabolized by the liver, guidance regarding alcohol consumption, and assessment of patient candidacy for major surgeries.

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