

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## The Relationship Between Hepatocellular Carcinoma and Hepatitis B and C Virus



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### **G&H** What is the current understanding of the role of hepatitis B and C virus in the setting of hepatocellular carcinoma?

**AK** We know that infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) can result in liver fibrosis, with the most extensive form of scarring known as cirrhosis. Through the process of fibrogenesis, cirrhosis puts patients at risk for hepatocellular carcinoma (HCC). In addition, HBV itself is known to be carcinogenic through multiple mechanisms of viral integration in the host genome, direct actions of HBV particles on host cells, and indirect mechanisms of inflammation leading to genetic damage over time. All of these processes can lead to oncogenesis in patients with HBV, even when they do not have cirrhosis.

HCV is also directly oncogenic, and although this virus does not integrate into the host genome, HCV proteins interact with numerous host-cell factors involved in cell signaling, transcription, proliferation, apoptosis, and transcription. Overall, however, HCC is uncommon in HCV patients without concomitant cirrhosis.

### **G&H** How significant is the risk of HCC from HBV or HCV infection?

**AK** Among noncirrhotic patients, the risk of HCC in patients with HBV infection increases with age. In Asian men younger than 40 years and Asian women younger

than 50 years, the risk of HCC is less than 0.2%. However, when considering HBV infection in Asian men aged 40 years and older and Asian women aged 50 years and older, as well as Africans of all ages, the risk of HCC is between 0.3% and 0.6% per year. Furthermore, the risk of HCC in HBV-infected patients continues to increase up to approximately 1% per year in patients who are 70 years and older.

When considering cirrhotic patients, the risk of HCC is substantially higher: 3% to 8% per year in patients with HBV and 3% to 5% per year in patients with HCV.

### **G&H** What is the incidence of HCV- and HBV-induced HCC in the United States?

**AK** The incidence of HCC and biliary cancers in the United States is approximately 8 per 100,000 persons, with at least 6 of these cases per 100,000 persons due to HCC. Among patients with HCC in the United States, 50% to 60% are infected with HCV and 10% to 15% with HBV. Of new cancer cases in the United States, HCC constitutes approximately 2% of cases and has been growing in incidence since the 1990s. This growth of HCC is primarily driven by the aging of people infected with HCV and subsequent development of cirrhosis. The recent development and approval of direct-acting antiviral (DAA) agents by the US Food and Drug Administration has dramatically simplified treatment for HCV with sustained virologic response (SVR) rates of more than 95%

(ie, “cure”) for most patient populations. However, an estimated 5 million Americans are infected with HCV, most of whom have not been treated and cured. Cure of HCV halts the progression of liver fibrosis, and reversal of fibrosis can even be seen in select patients, thereby decreasing the risk of HCC. Improved access and availability to DAA therapy can be expected to mitigate the growing HCC incidence.

### **G&H** What are the most common risk factors for HCC among HCV- and HBV-infected patients?

**AK** Risk factors for HCC among patients with HCV are cirrhosis, coinfection with HBV or HIV infection, alcoholic liver disease, increasing age, and male sex. Some studies have also suggested that concomitant diabetes, obesity, and infection with select HCV genotypes (1b or 3) may increase the risk for HCC.

The risk factors for HCC among patients with HBV are more complex. They include the host factors mentioned above for HCV (cirrhosis, male sex, increasing age, and alcoholic liver disease), family history of HBV, coinfection with HIV or hepatitis D virus, and exposure to aflatoxin. More recently, several single nucleotide polymorphisms have also been associated with the development of HCC.

There are also viral factors associated with the development of HCC in patients with HBV. These include evidence of ongoing hepatic injury, as shown by high serum alanine aminotransferase and/or aspartate aminotransferase levels, positive hepatitis B e antigen status, and higher HBV DNA levels (>2000 IU), with the risk of HCC increasing as the viral load increases. Other viral factors include HBV genotype D or B, as well as core promoter mutations.

### **G&H** Should all patients who have either HBV or HCV undergo screening for HCC?

**AK** This is a complex question. In general, surveillance for HCC has been deemed cost-effective in populations for which the incidence of HCC is greater than 0.2% per year for patients who have HBV, and greater than 1.5% per year in patients with HCV. Patient groups with HBV that meet this criterion are all patients with cirrhosis, African or North American blacks, HBV carriers with a family history of HCC, Asian men aged 40 years and older, and Asian women aged 50 years and older. Among patients with HCV, only those with known or suspected cirrhosis need to undergo surveillance for HCC.

Surveillance of these patients should entail at least an ultrasound of the liver every 6 months. Alpha-fetoprotein testing may also be used as an adjunct to ultrasound for HCC screening.

### **G&H** Does treating HBV or HCV reduce the risk of HCC?

**AK** In regard to HBV, studies of lamivudine and adefovir vs placebo have been shown to reduce the risk of HCC in patients with and without cirrhosis by up to 51%, data that are supported by meta-analyses. Currently, however, tenofovir and entecavir—both known to improve liver histology, reverse cirrhosis, and result in HBV viral suppression of more than 95% with a higher barrier to the development of viral resistance—are used as first-line agents for the treatment of HBV. Recently, one study evaluated the risk of HCC in patients treated with tenofovir and compared the incidence of HCC to the predicted incidence in that population by a risk calculator. Treatment of patients for 6 years with tenofovir significantly reduced the risk of HCC in noncirrhotic patients as compared with what would be predicted for that population over that period. There was no significant reduction in the risk of HCC among patients with cirrhosis in this study; however, very few patients with cirrhosis were included in the study. Similar results have been seen in patients treated with entecavir utilizing matched controls or risk calculators in Asian populations only. Larger studies of patients treated with tenofovir and entecavir for longer periods are needed in a US population, and I predict these will show results similar to those seen with previous lamivudine and adefovir studies—that is, a reduction in HCC in both cirrhotic and noncirrhotic patients.

As for the impact of HCV treatment on HCC risk, studies have shown that patients treated with interferon-containing therapies had a reduced risk of HCC, particularly patients who achieved SVR. In an analysis of 3 studies, patients had a 70% reduction in HCC and a 90% reduction in the risk of liver-related mortality and/or transplant.

### **G&H** Has there been any research on the risk of HCC specifically after the use of DAA agents in patients with HCV?

**AK** There are no data on the risk of HCC after the use of DAA agents for the treatment of HCV. However, there are several studies of long-term outcomes of DAA therapy ongoing at this time. Given that DAA agents have been shown to be so effective for the treatment of HCV, there will likely be a lot of data over the next few years regarding long-term survival, liver fibrosis, and transplantation, as well as the risk of HCC in patients who have been cured of their HCV with DAA therapies.

### **G&H** Does treating HCV or HBV while a patient has HCC impact disease recurrence?

**AK** One study has evaluated the efficacy of HCV treatment with DAA therapies in patients who also have HCC. In this single-center retrospective study, patients treated with DAA agents for their HCV who had Barcelona Clinic Liver Cancer (BCLC) stage 0 experienced higher rates of cure than patients with later-stage BCLC. Even though this study did not include long-term follow-up of the patients, the study is important because it is the only one to date that has used DAA agents to treat HCV in patients.

In regard to HCV therapy with interferon, studies have shown that achieving SVR at week 12 in patients with HCC is associated with increased overall survival and recurrence of HCC post–liver resection. It is likely that once long-term data are available on the treatment of HCV using DAA agents in patients with HCC, a similar positive effect will be seen on long-term outcomes.

In addition, the treatment of HBV with antiviral nucleotide analogues has been shown to reduce the risk of HCC recurrence after “curative” liver resection as well as after radiofrequency ablative therapy for HCC by approximately 10%.

**G&H** Does the treatment of HBV or HCV in patients with HCC affect Model for End-Stage Liver Disease scores or time to liver transplant?

**AK** There are no data on the effect on Model for End-Stage Liver Disease scores. However, one study did suggest that HCC patients who were cured of their HCV experienced a longer time on the transplant list, which would mean that their chances of receiving a transplant would be higher.

**G&H** Are there any other advantages to treating HBV or HCV in the setting of HCC?

**AK** We need more studies to fully understand the impact of HCV and HBV treatment on long-term survival, which is the most important primary outcome, as well

as on HCC outcomes, liver transplantation, and HCC recurrence. Such studies are needed in both patients with early-stage HCC as well as more advanced disease, as these are groups of patients with different prognoses.

In particular, given the high cost of DAA medications, the benefit of treating HCV in patients with a possible poor overall prognosis needs to be better defined. The key questions are whether we are able to prolong survival by treating HCV in patients, and whether this benefit is for all patients with HCV and HCC, or just select early-stage patients.

**G&H** Are there any special considerations that should be kept in mind when managing these patients?

**AK** It is important to be aware of potential drug-drug interactions between the new DAA agents for HCV and any concomitant HCC therapies. Although there are no contraindications to using these 2 sets of therapies at this time, DAA agents have been used in very few patients with concomitant HCC to date. Therefore, patients should be carefully monitored for any additional toxicities.

*Dr Kohli has no relevant conflicts of interest to disclose.*

**Suggested Reading**

Hsu YC, Ho HJ, Wu MS, Lin JT, Wu CY. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. *Hepatology*. 2013;58(1):150-157.

Kanogawa N, Ogasawara S, Chiba T, et al. Sustained virologic response achieved after curative treatment of hepatitis C virus-related hepatocellular carcinoma as an independent prognostic factor. *J Gastroenterol Hepatol*. 2015;30(7):1197-1204.

Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. *Cancer*. 2015;121(20):3631-3638.

Lee TY, Lin JT, Zeng YS, Chen YJ, Wu MS, Wu CY. Association between nucleos(t)ide analogue and tumor recurrence in HBV-related hepatocellular carcinoma after radiofrequency ablation [published online October 1, 2015]. *Hepatology*. doi:10.1002/hep.28266.

Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308(18):1906-1914.

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