

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Risk of Hepatocellular Carcinoma Using Tenofovir Disoproxil Fumarate Vs Entecavir for Hepatitis B Virus Treatment



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### **G&H** What is the current understanding of the relationship between hepatocellular carcinoma and hepatitis B virus infection?

**RW** Patients infected with chronic hepatitis B virus (HBV) are at increased risk of developing hepatocellular carcinoma (HCC) over time. There are 2 pathways from which HBV infection leads to HCC. The traditional and more common pathway is mediated through the development of cirrhosis, such that progressive HBV-related liver injury leads to accumulation of hepatic fibrosis and subsequently cirrhosis, which is associated with a significantly increased risk of HCC. The pathway from liver injury to accumulated hepatic fibrosis to cirrhosis and subsequent HCC is similar to that observed among other chronic liver diseases, such as hepatitis C virus, alcoholic liver disease, or nonalcoholic steatohepatitis. By far, the majority of HBV-infected patients who develop HCC progress through the pathway of cirrhosis.

However, HBV can also lead to HCC in patients without cirrhosis, and noncirrhotic HCC accounts for approximately 20% of HBV-related HCC. The underlying mechanism is due to the nature of HBV itself, as it is a DNA virus that can integrate into the host and, thus, has direct carcinogenic potential.

There have been different speculations as to which populations are at greater risk for noncirrhotic HBV-

related HCC. Certain genotypes of HBV have been demonstrated to have a more aggressive natural history, including disease progression to cirrhosis and HCC. However, there may be other risk factors as well, including insulin resistance or diabetes mellitus. As a result of these observations, current guidelines from the American Association for the Study of Liver Diseases recommend screening for HCC in HBV-infected patients with cirrhosis, as well as in subsets of patients without cirrhosis at particularly higher risk, including Asian or black men over the age of 40 years and Asian women over the age of 50 years.

### **G&H** How does HBV treatment (eg, with tenofovir disoproxil fumarate or entecavir) affect the risk of HCC?

**RW** Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir are first-line therapies for chronic HBV infection. All 3 of these treatments are fairly similar in their effectiveness in suppressing HBV DNA and normalizing alanine aminotransferase (ALT). Over the last several years, there has been an explosion of interest in exploring whether there is a difference in the risk of HCC in patients who have been treated with these drugs. In particular, several studies have specifically focused on differences in HCC risk associated with TDF and entecavir. Although a number of studies have shown

a strong signal for a lower risk of HCC in patients treated with TDF than in those treated with entecavir, there have

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also been similar studies showing no difference in HCC risk between these 2 therapies.

Several hypotheses have been raised in attempting to explain the conflicting results of these studies. Differences in methodologies as well as differences in the characteristics and demographics of the study cohort have been raised as potential sources of the different observations. For example, some studies have suggested that cohorts in Asia have a higher overall risk of HCC, predominantly because HBV-infected patients from that region are more likely to have HBV with genotype B or C, which may correlate with greater carcinogenic potential in developing HCC. In one of the largest studies on this issue, which was published in *Gastroenterology* this year, over 29,000 patients in Hong Kong with HBV infection were evaluated to determine whether HCC risk differed by HBV treatment. This study observed that patients treated with TDF had a lower HCC risk than patients treated with entecavir. Although some people have hypothesized that this difference may be reflective of the primarily Asian cohort that was evaluated, other studies with predominantly Asian populations have shown different results. For example, a Korean study published last year in the *Journal of Hepatology* evaluated a smaller cohort of nearly 3000 patients with HBV infection from 2012 to 2014. The investigators observed no differences in HCC risk between patients treated with TDF or those treated with entecavir. Interestingly, these findings are contrasted with another Korean study, which was published in *JAMA Oncology* last year, that did show a difference in HCC risk, specifically a lower risk of HCC in TDF-treated patients

compared to entecavir-treated patients. These disparate findings continue to raise important questions about whether there is indeed an actual difference in HCC risk, in which populations is this risk difference clinically significant, and what are the potential etiologies that may explain this difference.

#### G&H What have studies on other populations found?

**RW** Although much of the focus has been on Asian populations, there have been several important studies that have been conducted on non-Asian populations. A multinational study, published earlier this year in the *American Journal of Gastroenterology*, included 19 centers and a cohort of approximately 5500 patients with chronic HBV infection. This study included patients from the United States in addition to Korea, Japan, China, Hong Kong, and Taiwan, thus incorporating non-Asian patients infected with HBV. The investigators observed no difference in HCC risk by HBV treatment.

Most recently, a study from Europe published in the *Journal of Hepatology* also evaluated differences in HCC risk. This study, which included 1935 white patients infected with HBV, is important because it specifically focuses on a predominantly non-Asian cohort that has not been previously evaluated in detail. Over a 5-year period, the risk of developing HCC was 6% in patients treated with TDF and 5.4% in patients treated with entecavir. After adjustments with multivariate modeling, no difference was found in the long-term risk of HCC between the 2 groups. The findings from this study highlight the persisting questions about whether differences in HCC risk exist and among which populations are these differences most pronounced.

#### G&H How, more specifically, do the designs of these studies differ, and what are their main limitations?

**RW** The main limitation of all of these studies is the retrospective observational designs that evaluate patients in whom HBV treatment decisions have already been made to then evaluate whether these differences in HBV treatment choice translate into differences in HCC risk. As such, despite employing sophisticated methodologic approaches to try and address potential biases and confounding, there remain risks of residual bias and unmeasured confounders as well as aspects of treatment decisions that are not easily captured via retrospective observational approaches.

In addition, some of these studies have used large claims databases, which generally have limited granular

data to allow for exploration of potentially important details that may differ between treatment groups. Other studies have used clinical data from country- or territory-specific health care databases. This type of study often has more detail in terms of the granular clinical aspects that are needed to understand the implications of the outcomes, but still has limitations because it is observational and based on electronic health care record data. For example, missing data or baseline differences between groups and the validity of the approaches to address these data issues are important limitations to consider when evaluating the outcomes of these studies.

Different statistical methods have been applied in many of these studies to try to correct for potential differences. Important questions that have arisen in some studies include: Are the patients who were treated with TDF different from those who were treated with entecavir? Are there inherent differences in, for example, clinical characteristics, patient demographics, care received by patients, time to treatment, and response to treatment? Are there inherent differences that are contributing to the HCC outcomes that were observed? Some studies have used adjustments in multivariate modeling to try to adjust for potential factors that may affect or confound the association between treatment choice and HCC. Other studies have used propensity score matching or inverse propensity score weighting. These methods use a variety of different clinical and demographic inputs to calculate the likelihood of a certain patient infected with HBV being treated with a particular agent. Such an adjustment attempts to simulate a randomized trial to try to balance differences between the groups.

However, many people have questioned whether the contrasting findings from these studies are due to differences in baseline risk that were not adequately adjusted because of the persistence of unmeasured confounders in observational studies. Although statistical methods can be used to try to correct for confounders, they are imperfect. For example, studies have noted treatment or nontreatment, but not whether there were delays in treatment and how long patients were monitored before treatment started. Some studies did not have much data on evaluating response to treatment or differences in HBV genotype or quantitative surface antigen levels. All of these factors may offer some clues as to why certain populations may have a lower risk of HCC with TDF vs entecavir.

**G&H** Could the differences between the drugs themselves explain why they might be associated with a different risk of HCC?

**RW** Much has been speculated about whether the differences between the drugs are clinically relevant and

whether they impact the risk of HCC. These differences include the mechanism of action, as entecavir is a nucleoside analog whereas the tenofovir family of drugs are nucleotide analogs. Although data are limited, several studies have shown that nucleotide analogs trigger a larger response in stimulating interferon- $\lambda$ 3 levels, which

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are important for suppressing the hepatitis B viral load and surface antigen. However, it has not been explored further whether this translates into clinical outcomes such as HCC or disease progression. In addition, some studies have suggested that nucleotide analogs are more effective and quicker in suppressing hepatitis B surface antigen levels, but further research is needed.

Another difference that has been discussed as potentially contributing to variations in HBV outcomes is antiviral resistance. Although both TDF and entecavir are very effective in suppressing HBV DNA and normalizing ALT, long-term studies have reported antiviral resistance of up to 1.2% at 5 years among nucleoside-naive patients treated with entecavir. This is contrasted with reported antiviral resistance of 0% for up to 8 years in TDF-treated patients. This is particularly important for patients who have been exposed to other therapies, such as lamivudine, and thus carry a higher risk for developing resistance patterns. These factors may end up having some significance as we learn more about the drivers of clinical differences in HBV-related outcomes.

**G&H** Do you think TAF will likely have the same impact on HCC risk as TDF?

**RW** TAF is a newer formulation of tenofovir that has recently become available for clinical treatment of chronic HBV infection. The benefit of TAF is a more

advantageous safety profile, particularly with respect to bone disease and renal disease. However, both TAF and TDF are prodrugs that lead to the active tenofovir agent. As such, it would be reasonable to expect that HCC risk reduction in TAF would be similar to that observed in TDF-treated patients.

### G&H Is entecavir carcinogenic?

**RW** This is somewhat of a controversial issue. Some animal models have suggested that entecavir itself may have slight carcinogenic potential. However, this has not been confirmed by subsequent studies, nor has it been confirmed in human ones. Thus, the current consensus is that entecavir itself likely does not play a major role in actively contributing to HCC.

### G&H What further research is needed?

**RW** Further studies related to elucidating differences in HCC risk in HBV-infected patients should focus on the potential mediating factors posed by HBV genotype and quantitative surface antigen. In particular, it would be interesting to understand whether differences in HCC risk attributed to different HBV therapies are correlated with differences in effectiveness in suppressing quantitative surface antigen levels, or whether the rapidity of HBV DNA suppression or ALT normalization may also contribute to differences in HBV outcomes.

Personally, I do think that there is likely a difference in HCC risk that is associated with different HBV therapies. However, I do not think that this HCC risk difference is clinically relevant in all populations. Future studies should focus on better understanding the mechanistic drivers of the difference in HCC risk, which will help guide development of prediction models to individualize HBV treatment to achieve the greatest reduction in disease progression to cirrhosis and HCC.

### G&H Before guidelines are changed, should there be a randomized, controlled trial?

**RW** I do not think that a randomized, controlled trial comparing different HBV treatments will be pursued with the current data that are available. As previously mentioned, TDF, TAF, and entecavir are effective at reducing and normalizing ALT as well as suppressing HBV DNA. Ultimately, I think future efforts in HBV therapeutics should be focused on developing novel agents that will allow us to better achieve surface antigen loss and functional cure. Achieving functional cure will more significantly alter the epidemiology of chronic HBV and reduce long-term risk of cirrhosis and HCC.

#### Disclosures

*Dr Wong has received research grants from, performed consulting for, and been on the advisory board and speakers bureau for Gilead Sciences.*

#### Suggested Reading

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