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#### Conflicts of interest

The authors disclose no conflicts.

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0016-5085/\$36.00

<http://dx.doi.org/10.1053/j.gastro.2014.05.027>

## Averting Hepatocellular Carcinoma in Chronic Hepatitis B With Antiviral Therapy: Tipping the Balance or Not Yet?

See “Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B—a nationwide cohort study,” by Wu C–Y, Lin J–T, Ho HJ, et al, on page 143; and “Mortality, liver transplantation, and hepatocellular carcinoma among patients with chronic hepatitis B treated with entecavir vs lamivudine,” by Lim Y–S, Han S, Heo N–Y, et al, on page 152.

One of the most severe complications of chronic hepatitis B virus (HBV) infection is the development of hepatocellular carcinoma (HCC). The incidence of HCC in Western countries has risen considerably in the recent years and latest statistics from World Health Organization on trends in cancer incidence and mortality show that liver cancer has moved up to one of the leading causes of death worldwide.

Licensed oral antiviral agents for chronic HBV infection are the nucleos(t)ide analogs (NUCs), lamivudine, adefovir, telbivudine, entecavir, and tenofovir. Initially, goals in terms of treatment success were decline of HBV DNA levels but with more potent drugs and longer treatment duration, milestones for treatment have become more solid and clinically relevant. Reducing the risk of HCC is one of these milestones. NUC therapy seems to be beneficial in this regard and articles by Wu et al<sup>1</sup> and Lim et al<sup>2</sup> in this issue of *Gastroenterology* deliver stimulating evidence rendering feasible benefits for prevention of HCC secondary to treatment with NUCs.

The article by Wu et al<sup>1</sup> shows the impact of NUC induced risk reduction for HCC in a large, nationwide cohort of chronic HBV patients. This retrospective study from Taiwan analyzed the risk of HCC in patients treated with either lamivudine, entecavir, telbivudine, or >1 NUC for ≥90 days, whereas the control population received a hepatoprotective agent only. Propensity scores were used to match the populations. The NUC-treated cohort had a significantly lower 7-year incidence of HCC compared with controls. The large cohort contributed to the strength of the study making it possible to assess the various subgroups and to identify which group amongst them benefited the most in terms of reduced risk of HCC. Overall, the effect of NUCs on reduced risk for HCC was stronger in young patients without cirrhosis and in patients without diabetes mellitus. The major limitation of this study is that it was based

on retrospective observational data and may be subject to selection bias and confounding factors. Another limitation is the absence of baseline information regarding alanine aminotransferase and HBV DNA levels, which makes calculation of HCC risk using the recently developed HCC scores impossible.

The second article by Lim et al<sup>2</sup> is also a retrospective analysis of data comparing mid-term clinical outcome of chronic HBV patients, treated with entecavir or lamivudine at tertiary care hospital in Seoul, Korea. This study, also using propensity score matched cohorts, shows that patients in entecavir group had a significantly lower risk of death or transplantation than those treated with lamivudine, but there was no difference in risk for HCC between the 2 treatment groups. The paper provides further evidence for the persistent risk of HCC in HBV patients treated with even the most potent agents. The strengths of this study were its relatively large size and the fact that follow-up was rather complete with limited missing data. Major limitation of this study was the shorter duration of treatment and follow-up in the entecavir group, which may have prevented the authors from detecting a significant difference in reduced risk of HCC between this group and lamivudine. Use of rescue therapy with add-on adefovir in the lamivudine treated group is another potential explanation due to which treatment with entecavir did not reduce the HCC risk to a greater extent than lamivudine. Lastly, this was a single-center study, which limits the generalizability of the results.

The best way to assess the ability of reducing HCC with antiviral therapy is to perform a prospective, randomized, controlled trial. Liaw et al<sup>3</sup> performed such a study about 10 years ago. In this study, patients were randomized to either lamivudine or placebo. The study reported a clear reduction in the composite endpoint of liver complications (cirrhosis, liver failure, and HCC) in the lamivudine group compared with placebo. Although this study suggested a reduction in the incidence of HCC within the lamivudine treated group, it was not significant after the analysis was corrected for the time to diagnosis of cancer ( $P = .052$ ). The evidence that antiviral therapy is beneficial to reduce and even reverse cirrhosis<sup>4</sup> and liver failure<sup>5</sup> is currently so compelling that it is not considered ethical anymore to repeat such a placebo-controlled study with HCC as an endpoint. This could potentially be done in an immunotolerant patient with a very high viral load and no inflammation, but according to

the current guidelines therapy is not recommended in these patients. It is known that several of them will develop active inflammation and even HCC later in life. However, because the number of immunotolerant patients developing HCC is limited, a power analysis of such a study would probably dictate huge numbers of patients with lengthy follow-up.

We know that it is possible to almost fully prevent hepatic decompensation and portal hypertension in compensated cirrhosis with long-term NUCs, in particular entecavir and tenofovir. However, this is not the case for HCC, which can probably be reduced but definitely not fully prevented in HBV cirrhosis. A summary of the full papers published on HCC risk in HBV patients treated with NUCs is given in Table 1.

An important question that arises is whether the studies by Wu et al<sup>1</sup> and Lim et al<sup>2</sup> will change our practice of screening for HCC among viral-suppressed HBV patients. In clinical practice, the current consensus is that regular surveillance is imperative for patients in a high-risk category, such as older patients and those with cirrhosis (American Association for the Study of Liver Diseases, Asian Pacific Association for the Study of the Liver, and European Association for the Study of the Liver guidelines) regardless of antiviral treatment. The risk of HCC is just reduced and not fully eliminated with antivirals for several reasons. The most important one is that fragments of the viral genome may have integrated into the host genome, which could lead to genomic alterations and/or chromosomal instability, even before initiation of therapy.<sup>6</sup> Recently introduced HCC score calculators<sup>7</sup> can be used for risk prediction in both untreated and treated patients, although their validity is still limited in Caucasians because these models were developed on data from exclusively Asian patients. Because both papers in this issue of *Gastroenterology* come from the Far East, Caucasian patients with HBV genotype A or D are lacking. The majority of patients in the Korean paper have genotype C, which has been associated with an high risk of HCC. An attempt to study HCC risk reduction by antivirals in non-Asian patients is described in a recent study by Gordon et al,<sup>8</sup> which explored benefits of NUCs in a diverse US cohort; still, about half of them were Asian. The study demonstrated a 60% decrease in occurrence of HCC among patients who received antiviral therapy for chronic HBV infection compared with those who did not. This reduction was found across the spectrum of liver disease severity, viral loads, and ethnic backgrounds. However, other studies performed among mostly elderly Caucasians in Europe showed no or at most very limited reduction of HCC among both cirrhotic and noncirrhotic patients.<sup>9,10</sup> Taken together, it is important that the results of all Asian studies are further confirmed in non-Asian cohorts before they could lead to new general screening recommendations in the international guidelines.

In conclusion, the articles by Wu et al<sup>1</sup> and Lim et al<sup>2</sup> in this issue of *Gastroenterology* provide a stepping stone with regard to the use of NUCs and associated lower incidence of HCC. The first paper shows that NUCs use is associated with reduced risk of HCC in chronic HBV patients compared with no treatment, particularly in younger, noncirrhotic patients, whereas the second paper shows equivocal risk in terms of preventing HCC in entecavir- and lamivudine-treated

**Table 1.** Literature on HBV-Related HCC Prevention by NUCs (Full Original Papers Only)

Author	Study Design	Patient Groups (Treated vs Control)	Treatments	Follow-up (y)	Cumulative Incidence Rate of HCC at 5 y (% Treated vs % Control)	Relative Risk/Risk Difference (95% CI)	P Value
Wu et al <sup>1</sup> (Taiwan)	Retrospective (PS matched)	21,595/21,595	Different NUCs vs hepatoprotective agent	3.4/5.2	7.3/22.7 7-year incidence	0.31 (0.27–0.53)	<.001
Lim et al <sup>2</sup> (Korea)	Retrospective (PS Matched)	1,792/1,792	ETV vs LVD	3.1/8.7 <sup>a</sup>	NS	1.08 (0.87–1.34)	.48
Liaw et al <sup>3</sup> (Asian Pacific Region-multiple centers)	Prospective, randomized, controlled trial	436/215	LVD vs placebo	2.7	3.9/7.4	0.49	.047
Wong et al <sup>5</sup> (Hong Kong)	Retrospective/prospective	1,446/424	ETV vs no treatment	3.0/9.5	6.6/6.5	0.55 (0.31–0.99)	.049
Gordon et al <sup>8</sup> (United States)	Retrospective (PS matched)	820/1,851	NUC ± IFN vs no treatment	5.2	2.4/2.5	0.39 (0.27–0.56)	<.001
Hosaka et al <sup>11</sup> (Japan)	Retrospective (PS matched)	316/316	ETV vs no treatment	3.3/7.6 <sup>a</sup>	3.7/13.7	0.37 (0.15–0.91)	.03
Kumada et al <sup>12</sup> (Japan)	Retrospective (PS matched)	117/117	Different NUCs vs no treatment	12.3/11.6	2.7/11.3	0.28(0.13–0.62)	.002
Kobashi et al <sup>13</sup> (Japan)	Prospective, nonrandomized trial	129/127	ETV vs LVD	2.9/6.0 <sup>a</sup>	11.8/11.7	—	NS

ADV, adefovir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; ETV, entecavir; LdT, telbivudine; PS, propensity score; LVD, lamivudine; NS, not significant; NUCs, nucleos(t)ide analog.

Continuous variables presented as mean values, unless stated otherwise.

<sup>a</sup>Median.

patients. Both papers support the accumulating evidence that to avert the risk of HCC, viral replication needs to be inhibited early during the chronic HBV infection, preferably before the stage of advanced fibrosis.

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### Conflicts of interest

The authors disclose no conflicts.

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<http://dx.doi.org/10.1053/j.gastro.2014.05.026>

## Studies in Human Intestinal Tissues: Is It Time to Reemphasize Research in Human Immunology?

See “A CD3-specific antibody reduces cytokine production and alters phosphoprotein profiles in intestinal tissues from patients with inflammatory bowel disease,” by Vossenkämper A, Hundsrucker C, Page K, et al, on page 172.

Inflammatory bowel diseases (IBD) arise largely owing to an inappropriate mucosal immune response to

luminal antigens.<sup>1,2</sup> Our understanding of the pathogenesis of these diseases and many of our current and future therapeutic approaches, have evolved from studies of human tissues and animal models. In this issue of *Gastroenterology*, Vossenkämper et al,<sup>3</sup> reported on their investigation of the ability of an antibody targeting CD3 to inhibit T-cell-mediated inflammation in intestinal tissues from patients with ulcerative colitis (UC) or Crohn’s disease (CD). This interesting study illustrates the potential benefit of studying