Original Article

Impact of Long-Term Tenofovir Disoproxil Fumarate on Incidence of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B

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BACKGROUND: Efficacy trials have shown that antiviral therapy improves the outcomes of patients with chronic hepatitis B virus (HBV) infection. However, prospective data regarding the effect of antiviral therapy on the incidence of hepatocellular carcinoma (HCC), especially among patients without cirrhosis, are limited. The authors examined the impact of tenofovir disoproxil fumarate (TDF) on the incidence of HCC using a validated prediction model. **METHODS:** The incidence of HCC in patients treated with TDF was obtained in the pivotal TDF registration studies after 384 weeks of follow-up. The predicted risk of HCC in individual patients was calculated using the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model, which estimates HCC incidence for up to 10 years based on age, sex, alanine aminotransferase level, hepatitis B e antigen status, and HBV-DNA. Standardized incidence ratios (SIRs) were calculated comparing the observed and predicted numbers of HCC cases in the study cohort. **RESULTS:** Among 634 patients with evaluable baseline biopsies, 152 had cirrhosis (Ishak fibrosis score of 5 or 6) and 482 did not. During the 384 weeks of study, 14 cases of HCC were reported, with 4 occurring within the first year. The incidence of HCC was 0.37% per year in the study as a whole (0.28% among patients without cirrhosis and 0.65% among patients with cirrhosis). Among patients without cirrhosis, the observed incidence of HCC was significantly lower than predicted (SIR, 0.40; 95% confidence interval, 0.199-0.795). The last HCC case in a patient with cirrhosis occurred around week 192 with an SIR of 0.51 (95% confidence interval, 0.231-1.144) reported at week 384. **CONCLUSIONS:** Based on the REACH-B risk calculator, long-term therapy with TDF was associated with a reduced incidence of HCC among patients without cirrhosis who met treatment criteria. *Cancer* 2015;121:3631-8. © 2015 American Cancer Society.

KEYWORDS: antiviral therapy, chronic hepatitis B, hepatocellular carcinoma, REACH-B, tenofovir disoproxil, fumarate.

INTRODUCTION

With approximately 240 million individuals with chronic infections globally, hepatitis B virus (HBV) is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[1,2] Despite widespread implementation of universal vaccination, chronic hepatitis B (CHB) continues to be a major public health problem.

In a given patient, factors including male sex, presence of cirrhosis, diabetes, environmental exposures (eg, alcohol, smoking, and aflatoxin), and family history affect HCC risk.[3-5] In recent data, HBV-DNA levels, hepatitis B e antigen (HBeAg) status, and HBV genotype were reported to be associated with HCC development,[3] with the presence of cirrhosis and high HBV-DNA levels considered major drivers of HCC risk.[3,6,7] In light of the variability of HCC risk in individual patients,[8] several nomograms have been developed to assess a patient's risk of HCC.[9-11] The Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model uses age, sex, HBeAg status, and serum alanine

aminotransferase (ALT) and HBV-DNA levels to estimate a patient's HCC risk up to 10 years if untreated.[10] It was developed in patients without cirrhosis and validated in a multicenter hospital cohort that included patients with cirrhosis.

Several agents currently are approved for the treatment of CHB, including interferon-α and nucleos(t)ide analogues (NA)s. Several large randomized controlled trials have shown that antiviral therapy can lead to improvement in serum aminotransferase levels, HBeAg loss, hepatitis B surface antigen loss, a reduction in HBV-DNA levels, improvement in liver histology, and regression of cirrhosis.[12,13] Anti-HBV therapy has been associated with a reduced risk of HCC.[14] However, to the best of our knowledge, studies to date have shown benefits limited to patients with cirrhosis, with the majority of those data derived from retrospective studies based on patients clinically selected for antiviral therapy. Whether antiviral therapy confers beneficial effects on HCC in patients without cirrhosis, and how long after treatment initiation these effects may occur, are to our knowledge, undefined.

Ideally, a long-term placebo-controlled trial would provide the most definitive answers regarding anti-HBV therapy in the development of HCC. Given the well-accepted benefits of therapy, placebo-controlled trials would be unethical, at least in patients who are candidates for treatment according to various guidelines. Herein, we used data from the registration trials for tenofovir disoproxil fumarate (TDF) to assess the impact of antiviral therapy on the occurrence of HCC, focusing on patients without cirrhosis. We used the REACH-B model to estimate the expected incidence of HCC had trial participants not been treated.

MATERIALS AND METHODS

Study Design

Data from TDF registration studies GS-US-174-0103 (HBeAg-positive; ClinicalTrials.gov identifier NCT00116805) and GS-US-174-0102 (HBeAg-negative; ClinicalTrials.gov identifier NCT00117676) were used.[15,16] Patients provided informed consent and the study was approved by the ethics committees of the participating institutions. Patients aged 18 to 69 years were randomized 2:1 to receive TDF or adefovir dipivoxil (ADV) for 48 weeks in a double-blinded manner, followed by open-label TDF for up to 384 weeks. Race was based on self-report. Patients were required to be positive for hepatitis B surface antigen for ≥6 months before enrollment with evidence of active HBV infection (ie,

detectable HBV-DNA and elevated ALT). Patients with cirrhosis (Ishak fibrosis scores of 5 or 6) were included in the studies. Patients with a history of HCC or prior clinical hepatic decompensation were excluded. No patient experienced hepatic decompensation during the current study. Liver biopsies were performed at baseline and at weeks 48 and 240 and were evaluated using the Knodell and Ishak scoring systems by a single independent pathologist blinded to patient treatment and visit number.

Although virologic efficacy was the primary endpoint of the current study, participants continued to receive routine care at each site, including screening, diagnosis, and treatment for HCC according to local practice guidelines and conventions. Although HCC was not a prespecified study endpoint, it was captured as a predefined adverse event. The current analyses are based on data obtained at week 384.

Statistical Analysis

Standard descriptive statistics of patients by baseline cirrhosis status were conducted. Observed HCC incidence along with 95% confidence intervals (95% CIs) were calculated using the Kaplan-Meier method stratified by baseline cirrhosis status.[17]

Predicted HCC incidence was calculated using REACH-B,[10] a Cox regression model relating HCC risk to sex, age, ALT level, HBeAg status, and DNA level. We obtained coefficients of the Cox model and baseline disease-free survival at years 3, 5, and 10 from Yang et al.[10] Detailed survival estimates in yearly increments from 1 to 10 were obtained from the REACH-B authors. We used linear interpolation to estimate the baseline disease-free survival for events occurring between full calendar years.

REACH-B estimates the numbers of HCC cases as follows. The HCC-free survival probability in patient i at time t is

$$S_i(t) = [S_{0i}(t)]^{\exp(X_i\beta)}$$

in which $S_{0i}(t)$ is the baseline survival probability for patient i at time t, β is a vector of the coefficients from the REACH-B model, and X_i is a vector of the baseline characteristics of the patient. Expected number of events for a subject is

$$e_i = -\log_e\left(S_i(t)\right) = -\exp(X_i\beta)\log_e[S_{0i}(t)],$$

and summing these over all patients provides the predicted number of HCC cases during the follow-up:

TABLE 1. Baseline Characteristics of Patients by Cirrhosis Status[a]

Characteristic[b]	Patients With Cirrhosis (n = 152)	Patients Without Cirrhosis (n = 482)	P[c]
Mean age (SD), y	45.2 (10.6)	38.4 (11.8)	<.001
Male, no. (%)	123 (81)	345 (72)	.026
Race, no. (%)			.339
White	92 (61)	283 (59)	
Asian	39 (26)	148 (31)	
Other	21 (14)	51 (11)	
HBeAg positive, no. (%)	60 (39)	199 (41)	.706
Mean (SD) HBV-DNA, $\log_{10}$ copies/mL	7.6 (1.4)	7.7 (1.5)	.289
Mean (SD) ALT, U/L	143.2 (123.4)	143.0 (113.1)	.714
HBV genotype			.043
A	34 (22)	67 (14)	
B	10 (7)	64 (13)	
C	27 (18)	83 (17)	
D	73 (48)	239 (50)	
Other	8 (5)	29 (6)	

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; SD, standard deviation.
[a] Cirrhosis was defined as an Ishak fibrosis score of 5 or 6.
[b] 7 patients did not have baseline biopsy data available.
[c] Two-sided P values. The Wilcoxon rank sum test was used for continuous variables and the Fisher exact test was used for categorical variables.

$$\sum_{i=1}^{N} e_i = \sum_{i=1}^{N} -\log_e\left(S_i(t)\right) = \sum_{i=1}^{N} -\exp(X_i\beta)\log_e\left[S_{0i}(t)\right].$$

Standardized incidence ratios (SIRs) were calculated as a ratio of observed over predicted HCC cases in the studies for particular time intervals. The 95% CIs were calculated by Poisson regression without covariates with an offset equal to $\log_e$ (number of predicted cases).[18] Exposure time for subjects who dropped out prematurely is from baseline to the time of dropout (ie, predicted HCC cases reflected the number of subjects "at risk" at a given time point and are not based on the initial sample size).

Our primary analysis compared the observed versus predicted HCC incidence in patients without cirrhosis. SIRs were calculated over 384 weeks, with additional sensitivity analyses of patients with cirrhosis and Asian patients, and the exclusion of those who had HCC diagnosed during the first calendar year of the study. We also considered other HCC prediction models, including the CU-HCC (Chinese University-Hepatocellular Carcinoma) and GAG-HCC (Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis-Hepatocellular Carcinoma) risk scores to further validate our findings.[9,11] Last, we examined whether REACH-B applied to post-48-week on-treatment data matches the observed HCC cases. SIRs and 95% CIs were calculated as described above.

TABLE 2. Baseline Characteristics of Patients Who Developed HCC Compared With Those Who Did Not

Characteristic	HCC (n = 14)	No HCC (n = 627)	P[a]
Mean (SD) age, y	52.1 (10.6)	39.6 (11.8)	<.001
Male, no. (%)	12 (86)	461 (74)	.538
Race, no. (%)			.347
White	6 (43)	374 (60)	
Asian	6 (43)	183 (29)	
Other	2 (14)	70 (11)	
Median Ishak fibrosis score (range)	4 (2–6)	3 (0–6)	.023
Cirrhosis (%)[b]	6 (43)	146 (24)	.113
HBeAg positive, no. (%)	4 (29)	262 (42)	.416
Mean (SD) HBV-DNA, $\log_{10}$ copies/mL	7.0 (1.6)	7.7 (1.5)	.120
Mean (SD) ALT, U/L	101.1 (62.0)	143.4 (115.9)	.094
HBV genotype			.034
A	0 (0)	103 (16)	
B	2 (14)	72 (11)	
C	4 (29)	108 (17)	
D	5 (36)	310 (49)	
Other	3 (21)	34 (5)	

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; SD, standard deviation.
[a] Two-sided P values. The Wilcoxon rank sum test was used for continuous variables and the Fisher exact test was used for categorical variables.
[b] Cirrhosis was defined as an Ishak fibrosis score of 5 or 6.

RESULTS

Among 641 patients randomized and treated in studies 102 and 103, 7 individuals did not have sufficient histological data for inclusion in the current analysis. Of the remaining 634 patients, 482 did not have cirrhosis (76%) whereas 152 patients (24%) had cirrhosis at baseline (Table 1).

A total of 14 HCC cases were observed. Timing and characteristics of the HCC cases are summarized in Supporting Information Figure 2 and Table 2. Of the 14 cases, 9 patients were HBeAg negative, 6 had cirrhosis at baseline (all Ishak fibrosis score 6), and 12 patients were male (Supporting Information Table 1).

The annual HCC incidence in the study as a whole was 0.37% (95% CI, 0.20%-0.62%), and was 0.65% (95% CI, 0.24%-1.40%) among patients with cirrhosis and 0.28% (95% CI, 0.12%-0.56%) among patients without cirrhosis (Fig. 1). Known risk factors for HCC such as older age, advanced fibrosis/cirrhosis, and genotype C were observed when comparing those who did and did not develop HCC, although the small number of HCC cases reduces the power of the analysis (Table 2). There was no indication that variables such as high HBV-DNA or ALT levels influenced the incidence of HCC in these patients treated with an effective antiviral agent.
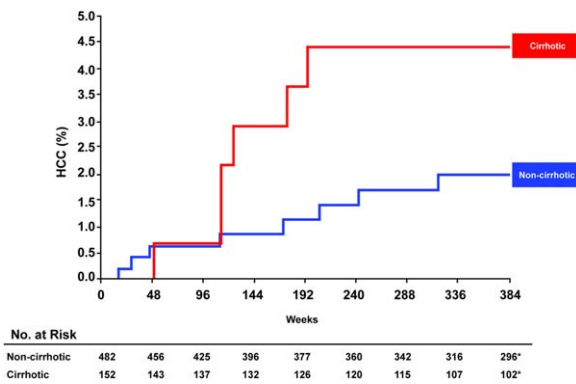
Figure 1. Observed incidence of hepatocellular carcinoma (HCC) by baseline cirrhosis status in studies 102 and 103. All 14 cases of HCC were depicted in this plot. Overall, the incidence of HCC in studies 102 and 103 was 37.0 per 10,000 person-years (0.37% per year), whereas among patients with cirrhosis the incidence was 64.5 per 10,000 person-years (0.65% per year) and among patients without cirrhosis, the incidence was 28.4 per 10,000 person-years (0.28% per year). *Asterisk indicates patients completing 384 weeks in the study as defined by protocol; 4 of 402 patients completing week 384 did not have baseline biopsy data available.

TABLE 3. REACH-B Estimation of HCC Cases for Patients Without Cirrhosis[a]

Time of Incident Week (Year)	Cumulative HCC Cases			
	Predicted	Observed	SIR	95% CI
17.3 (0.33)	0.74	1	1.36	0.191–9.622
28.1 (0.54)	1.19	2	1.68	0.421–6.727
46.1 (0.88)	1.92	3	1.56	0.503–4.835
111.7 (2.14)	5.03	4	0.80	0.299–2.120
172.3 (3.30)	6.79	5	0.74	0.307–1.769
206.0 (3.95)	8.63	6	0.70	0.312–1.548
242.4 (4.65)	11.45	7	0.61	0.292–1.283
318.1 (6.10)	16.62	8	0.48	0.241–0.963
End of week 384[b]	20.11	8	0.40[c]	0.199–0.795

Abbreviations: 95% CI, 95% confidence interval; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio.
[a] The observed time each case was detected is shown along with the predicted and observed number of cases. SIRs and 95% CIs are also provided.
[b] The median follow-up was 7.36 years (range, 0.00–7.55 years).
[c] Statistical significance at alpha = .05 (P = .009).

Table 3 presents observed and predicted cases of HCC among patients without cirrhosis. Three patients developed HCC within the first 48 weeks of randomization. By the time the third case occurred, REACH-B predicted 1.92 HCCs to have developed, which translated to an SIR of 1.56 (95% CI, 0.50-4.84), indicating that there were 1.56 times more HCC cases than expected. Subsequently, the SIRs dropped below 1, indicating a lower-than-expected HCC incidence. The SIRs progressively decreased and by the time the eighth patient with HCC was diagnosed, the SIR was 0.48 (95% CI, 0.24-0.96) and was statistically significant. At the end of the 384 weeks of follow-up, 20.11 cases were predicted by the REACH-B model compared with 8 observed cases. At that time point, the SIR was 0.40 (95% CI, 0.20-0.80), representing a 60% reduction in HCC incidence (Fig. 2 Top).

Table 4 compares the observed number of HCCs in patients with cirrhosis and what would be predicted by the REACH-B score. For the 6 HCC cases in this group of patients, the SIR ranged from 0.69 to 1.32. It is interesting to note that there were no new HCC cases observed in this group after the sixth patient was diagnosed around week 192 (Fig. 2 Bottom). As of the end of the follow-up (week 384), the SIR was 0.51 (95% CI, 0.23-1.14), although it was not statistically significant.

Because the diagnosis of cirrhosis in the REACH-B study was made on clinical grounds rather than via a liver biopsy, we also considered using laboratory data to define cirrhosis as supplementary data for comparison. The main analyses in the current study were based on histological definitions of cirrhosis (Ishak fibrosis scores of 5 of 6). When a platelet count $<150\times10^3/\mu L$ or serum total bilirubin >2 mg/dL was used as a surrogate criteria for cirrhosis, greater than two-thirds of patients with cirrhosis (108 of 152 patients) were misclassified as not having cirrhosis, whereas <10% of patients without cirrhosis (43 of 482 patients) were categorized as having cirrhosis. If these laboratory criteria were used to exclude cirrhosis, the SIR in patients without cirrhosis would be 0.22 (95% CI, 0.10-0.50).

We conducted a sensitivity analysis of the 189 Asian patients (148 patients without cirrhosis, 39 patients with cirrhosis, and 2 with nonevaluable biopsies). During the follow-up, 6 patients developed HCC. At baseline, 1 patient had cirrhosis and 5 did not. The sixth case was diagnosed at 6.1 years of follow-up (SIR, 0.81; 95% CI, 0.36-1.81). At week 384, the SIR was reduced to 0.66 (95% CI, 0.30-1.48), indicating that the effect of TDF among Asian patients is in the same direction as the overall population, whereas the small number of events likely precluded statistical significance.

Results of a similar analysis among non-Asian patients are shown in Supporting Information Table 3.

In another sensitivity analysis (Supporting Information Table 4), we excluded patients who developed HCC during the first year of study, because it is likely that these tumors represented prevalent cases at the time of study enrollment. As expected, this reduced the SIRs; at week
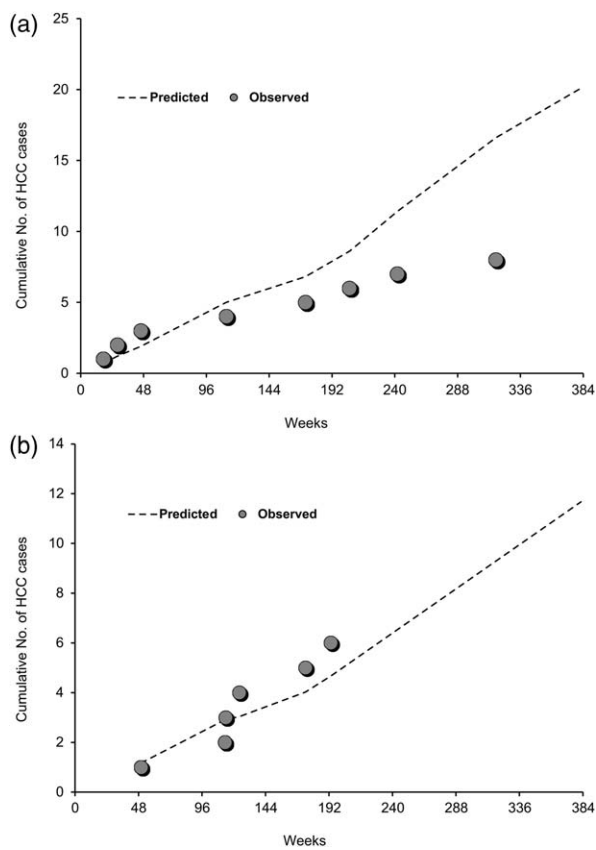
Figure 2. Observed hepatocellular carcinoma (HCC) cases versus predicted HCC incidence over time among patients (*Top*) without and (*Bottom*) with cirrhosis. (*Top*) The 8 cases of HCC observed (dots) in patients without cirrhosis were plotted against the predicted incidence of HCC (hashed line) using the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) algorithm over 384 weeks. At the time the eighth HCC case was observed, the standardized incidence ratio was 0.48 (95% confidence interval, 0.241-0.963). At the end of the 384 weeks, the standardized incidence ratio was 0.40 (95% confidence interval, 0.199-0.795), representing a 60% reduction in the incidence of HCC. (*Bottom*) The 6 cases of HCC observed (dots) among patients with cirrhosis were plotted against the predicted incidence of HCC (hashed line) using the REACH-B algorithm over 384 weeks. There were no additional cases observed after the case that occurred around week 192.

TABLE 4. REACH-B Estimation of HCC Cases for Patients With Cirrhosis[a]

Time of Incident Week (Year)	Cumulative HCC Cases		SIR	95% CI
	Predicted	Observed		
50.0 (0.96)	1.17	1	0.85	0.120–6.060
113.9 (2.18)	2.91	2	0.69	0.172–2.745
114.1 (2.19)	2.92	3	1.03	0.332–3.189
124.6 (2.39)	3.04	4	1.32	0.494–3.508
174.6 (3.35)	4.02	5	1.24	0.518–2.988
194.1 (3.72)	4.67	6	1.28	0.577–2.859
End of week 384[b]	11.67	6	0.51	0.231–1.144

Abbreviations: 95% CI, 95% confidence interval; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio.
[a] The observed time each case was detected is shown along with the predicted and observed number of cases. SIRs and 95% confidence intervals are also provided.
[b] The median follow-up was 7.36 years (range, 0.08–7.43 years).

low risk and 116 as being at high risk. It predicted 20.9 cases by year 5. Thus, the 2 models were consistent in suggesting that the risk of HCC in the patients in the current study was reduced by approximately one-third.

Supporting Information Table 2 examines the REACH-B prediction using on-treatment data. In studies 102 and 103, both HBV-DNA and ALT levels were greatly affected during the first 48 weeks of therapy. At week 48, the mean change in HBV-DNA was -5.20 $\log_{10}$ IU/mL (Wilcoxon signed rank, $P<.001$) in patients treated with TDF and -3.96 $\log_{10}$ IU/mL ($P<.001$) in patients treated with ADV, with no differences noted between patients with and without cirrhosis (-4.81 $\log_{10}$ IU/mL vs -4.71 $\log_{10}$ IU/mL, respectively; Wilcoxon rank sum, $P = .38$). ALT was significantly reduced in both groups, with 78.3% of patients treated with TDF and 72.6% of patients treated with ADV achieving normal ALT (Fisher exact test, $P = .13$). The percentage of patients with normal ALT at week 48 was also similar between patients with and without cirrhosis (71.5% and 78.4%, respectively; $P = .09$). HBeAg status was also significantly affected by antiviral therapy (percentage of HBeAg-positive patients: 41.5% at baseline vs 30.5% at week 48; $P<.001$). Obviously, the remaining parameters in the REACH B model, age and sex, were not affected by antiviral therapy. Using week 48 on-treatment data, the REACH-B model grossly underestimated the number of HCC cases. SIRs ranged between 1.91 and 3.89 for patients without cirrhosis, indicating that the prediction using on-treatment data underestimates the actual incidence by approximately 2-fold to 4-fold (Supporting

384, the SIR was 0.25 (95% CI, 0.10-0.60) in patients without cirrhosis and was 0.43 (95% CI, 0.18-1.03) in patients with cirrhosis.

A third sensitivity analysis considered the CU-HCC and GAG-HCC models to predict HCC occurrence (Supporting Information Table 5). The CU-HCC model classified 283 patients as being at low risk, 128 as being at intermediate risk, and 61 as being at high risk, predicting 22.5 HCC cases to occur by year 5. In comparison, we observed 13 HCC cases at year 5 in the current study. The GAG-HCC model categorized 356 patients as being at

Information Table 2). The magnitude of underestimation was even more dramatic in patients with cirrhosis (SIR range, 3.46-143.51).

DISCUSSION

Understanding the impact of antiviral therapy on HCC incidence in patients with CHB is important for both individual patient management and public health policy. The results of the current study demonstrate that HCC incidence in patients without cirrhosis treated with TDF was lower than expected. The effects of TDF became noticeable at approximately 2 years of therapy and eventually reached a SIR of 0.40, or a 60% reduction in incidence by week 384. Subsequent sensitivity analyses replicated the overall trend, further supporting the observation that TDF therapy is associated with HCC risk reduction.

HCC remains the most dreaded complication in patients with CHB. A major recent advance in our understanding of the natural history of HBV infection is the relation between serum HBV-DNA concentration and future risk of HCC.[7] This discovery was made in the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study, which prospectively followed a community-based cohort of untreated patients with HBV infection in Taiwan.[7] Derived from this cohort, the REACH-B model estimates HCC risk in patients without clinical evidence of cirrhosis.[10] It was subsequently validated in an external cohort from 3 hospitals located in Asia, including 18.4% of patients with cirrhosis.[10] To the best of our knowledge, the accuracy of models such as REACH-B in non-Asian populations is not established. A recent study of entecavir use on HCC reported low discriminatory performance in white individuals.[19] However, another study has suggested that the REACH-B model was accurate in a large North American cohort of patients with CHB with different genotypes.[20]

After initial data that suggested interferon therapy was associated with a reduced risk of HCC,[21] subsequent studies evaluated the effect of long-term NAs on HCC incidence. In what to our knowledge is the only randomized controlled trial conducted to date, lamivudine and placebo were compared in treatment-naive patients with advanced fibrosis/cirrhosis and active hepatitis.[22] After a mean treatment of approximately 3 years, lamivudine reduced the risk of HCC by 51%. Several nonrandomized studies, including a recent US study in a geographically and racially diverse study population, have shown a similar degree of risk reduction (ie, approximately 50%).[23] Another recent study demonstrated a benefit for NA

therapy in the postoperative prognosis of patients with HBV-related HCC.[24] Compared with these recent observational studies, the data from the current study are unique in that they were prospectively collected in a rigorous trial setting. The current study data also included baseline histological data to specifically identify patients without cirrhosis. Our results remained robust when cirrhosis was defined by surrogate clinical indicators, emulating the method by which REACH-B and other models were developed. Because the detection of cirrhosis in routine practice is neither sensitive nor standardized, noninvasive measurements of liver fibrosis by modalities such as transient elastography may help to enhance the accuracy of these models.

Cirrhosis is well established as a strong risk factor for HCC. It is likely that a part of the HCC risk reduction by antiviral therapy is associated with regression of fibrosis and cirrhosis, which have been demonstrated with long-term NA therapy.[12] In the data from the current study, HCC risk reduction was more pronounced in patients without cirrhosis, which suggests that suppression of viral replication has a direct impact on hepatic carcinogenesis independent of its effect on fibrosis. The current study data in patients with cirrhosis must be considered with caution for several reasons. First, the REACH-B model, based on patients without overt evidence of cirrhosis, most likely underestimates the incidence of HCC in patients with cirrhosis. One potential interpretation of our data may be that TDF therapy reduced the risk of HCC in patients with cirrhosis at least to the level expected in patients without cirrhosis. Second, it is likely that a longer observation may demonstrate continued HCC risk reduction.

The full impact of antiviral inhibition on HBV-related oncogenesis remains uncertain. Clearly, with potent NA therapy, HBV-DNA and ALT levels change promptly. Our 48-week on-therapy data suggest that HCC risk reduction did not parallel the rapid decrease in HBV-DNA or ALT and that it takes >1 year of therapy for the risk to be altered significantly. The data from the current study support a recent observational study that reported that risk scores decline during therapy and that the scores at baseline or after 1 year of therapy did not predict HCC incidence well,[19] although not all studies agree.[25] Ultimately, patients with active hepatitis meeting antiviral therapy indication remain at an increased risk of HCC, even when compared with those with inactive disease.[26] Clinicians and patients must remain vigilant regarding HCC surveillance in accordance with standard guidelines and taking into account individual risk factors,

even when appropriate HBV-DNA suppression and ALT normalization are achieved.[27,28]

There are limitations to the current study. Statistical power to demonstrate the desired effect of TDF therapy was limited by the small number of HCC cases despite the study's large denominator, which in and of itself is a result of TDF therapy substantially reducing HCC incidence. This limited our ability to conduct subgroup analysis. In the strictest sense, REACH-B is only applicable in Asian patients without cirrhosis. We reported only 5 Asian patients without cirrhosis who developed HCC. Although the sensitivity analysis of Asian patients without cirrhosis was not statistically significant, this and prior studies, including our analysis using the CU-HCC and GAG-HCC models, demonstrated a consistent effect of therapy, with an approximately one-third reduction in HCC. Second, HCC was not a predefined endpoint of the current study, and rather, was considered to be an adverse event. Although it is possible that the rigor with which HCC cases were reported may not have been as high as primary endpoints, there is no evidence in the current study to suggest systematic flaws in the diagnosis of HCC itself. We made random inquiries to select study sites to verify the practice of reporting HCC cases. There were no aberrant instances that would cause us to question the validity of an HCC diagnosis. Third, patients enrolled in clinical trials tend to have earlier stages of liver disease with lower risks of HCC, although approximately one-quarter of the individuals enrolled in the current study had cirrhosis (Ishak fibrosis score of 5 or 6) at baseline. However, the lack of an untreated control group makes this point difficult to evaluate.

The observed incidence of HCC in patients without cirrhosis who were treated with TDF was lower than that expected based on a well-validated prediction model, suggesting the benefits of antiviral therapy in reducing HCC beyond its impact on prevention and regression of fibrosis and cirrhosis. Although these are encouraging data for patients being treated with TDF, they must not be extrapolated to patients who do not meet current treatment criteria. Finally, HCC prediction models should not be applied using on-therapy data because they underestimate HCC incidence. Patients should continue to be monitored for HCC, following established guidelines, regardless of therapeutic response.

FUNDING SUPPORT

CONFLICT OF INTEREST DISCLOSURES

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