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The impact of nucleos(t)ide analog therapy in hepatitis B on the incidence of hepatocellular carcinoma: an update including recent literature findings

Walid S. Ayoub[1,2], Francis Dailey[1], Paul Martin[3,4], Patricia D. Jones[3,4]

[1]*Department of Gastroenterology and Hepatology, Cedars Sinai Medical Center, Los Angeles, CA 90048, USA.*
[2]*David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA.*
[3]*Division of Hepatology, Department of Medicine, University of Miami Miller School of Medicine, University of Miami, Miami, FL 33136, USA.*
[4]*Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL 33136, USA.*

Correspondence to: Dr. Walid S. Ayoub, Department of Gastroenterology and Hepatology, Cedars Sinai Medical Center, 8900 Beverly Blvd, Suite 250, Los Angeles, CA 90048, USA. E-mail: Walid.Ayoub@cshs.org

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ABSTRACT

Worldwide, hepatocellular carcinoma (HCC) is a significant cause of morbidity and mortality. In men, it is the fifth most common cancer and seventh most common in women; HCC is the second highest cause of cancer-related death worldwide. It is less prevalent in the USA and Northern Europe and more prevalent in Eastern and South-Eastern Asia. Over 700,000 cases are diagnosed each year - half of which occur in China - and result in roughly the same number of deaths per year. HCC significantly impairs quality of life and is associated with great costs to society. It is estimated that half of the deaths from HCC are associated with hepatitis B virus (HBV). Fortunately, HBV vaccination and antiviral therapy have shown excellent efficacy in decreasing the incidence of HCC. We will discuss the relationship of HBV to HCC, address available treatments for HBV and the impact of treatment on the development of HCC.

INTRODUCTION

Hepatitis B virus (HBV) is a DNA virus that incorporates into the host genome and thereby increases the risk of developing hepatocellular carcinoma (HCC). This risk of HCC is increased even in patients with HBV without cirrhosis; the risk of developing HCC is up to 100 fold higher in persons infected with hepatitis B compared to uninfected persons[1]. An effective strategy shown to decrease

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the incidence of HCC is vaccination against HBV. A recent analysis of two Taiwanese HCC registries of 1,509 patients diagnosed with HCC from 1983-2011 demonstrated an incidence per 10^5 person-years of 0.92 in the unvaccinated cohort and 0.23 in the vaccinated cohort[2]. Another appealing strategy to decrease the incidence of HCC in patients with chronic hepatitis B is inhibition of viral replication. In the seminal study by Liaw *et al.*[3], the chemopreventive effect of nucleos(t)ides was first suggested as the suppression of HBV replication led to decreased rates of cirrhosis, liver failure, and the development of HCC.

THE RELATIONSHIP BETWEEN HBV AND HCC

Chronic hepatitis B (CHB) stimulates the immune system to release cytokines and reactive oxygen species, which cause damage to genes, results in cell death and initiates a cascade of fibrosis. As a result, the hepatocyte cell cycle is accelerated and leads to accumulation of genetic alterations, which leads to malignant transformation of hepatocytes[4]. In addition, HBV integrates into the host DNA where it modifies the expression of certain oncogenes. Certain mutations have been implicated in contributing to a higher incidence of HCC. These include the HBV protein known as HBx, infection with HBV genotype C, the hepatitis B genome mutations pre-S deletions and core promoter mutations (V1735, T1762 and A1764)[4,5]. Another risk factor is the level of the hepatitis B surface antigen (HBsAg) titer. Levels of HBsAg that are greater than 1,000 IU/mL may independently predict increased risk for developing HCC in Asians in HBeAg negative patients with low HBV viral load[6]. One retrospective study examined the cumulative probability of HCC development over time despite long-term nucleos(t)ide analog (NA) therapy. The study included treatment-naive CHB patients (n = 524) who received treatment with NAs between January 2003 and December 2007 for longer than 48 weeks. The study revealed a cumulative probability of developing HCC at 1, 2, 3, 4 and 5 years of 0.2%, 1.8%, 3.6%, 5.8%, and 9.3% respectively. In multivariate analysis, age greater than 50 years [hazard ratio (HR) 1.05], family history of HCC (HR 5.48), and the presence of cirrhosis (HR 17.16) were significant predictors of HCC development. Importantly, maintaining a virologic response or HBV DNA < 20 IU/mL for longer than 12 months reduced the risk of HCC development (HR 0.09)[7]. These studies suggest that persistent HBV viral replication and subsequent liver injury are major risk factors for developing HCC.

The incidence of HBV-related HCC varies between the western world and Asia; the 5-year cumulative incidences of HCC in Asia among inactive carriers and those with compensated cirrhosis are 1% and 17%, respectively. In Europe and the United States, those incidences are 0.1% and 10%[8]. A recent meta-analysis evaluated 66 studies with a total of 347,859 patients using multivariate regression analysis, and after adjusting for age, there were no significant differences in HCC incidence between Western and European studies. The analysis showed that age, symptomatic carrier status, chronic hepatitis, or compensated cirrhosis were the greatest risk factors for development of HCC when compared to inactive carriers[9].

GOALS OF HBV THERAPY

There are 7 drugs currently approved for the treatment of CHB and they can be divided into 2 groups. The immune-modulators include pegylated interferon alfa-2a and interferon alfa-2b. The NA are oral medications, which include lamivudine, telbivudine, adefovir, tenofovir and entecavir. The oral agents have a better side effect profile and thus, most patients are treated with oral therapy. Goals of treating CHB in the short term include suppressing replication with induction of hepatitis B e-antigen (HBeAg) seroconversion in patients with HBeAg-positive CHB and normalization of alanine aminotransferase. In the long term, the goal is to achieve seroconversion of HBsAg to hepatitis B surface antibody. However, HBsAg seroconversion is not common with currently available therapies. It is seen in 1% and 1.5% of patients after 52 weeks of lamivudine or telbivudine therapy respectively. Furthermore, 5 years of adefovir therapy results in HBsAg loss in only 3% of patients. The rates of HBsAg seroconversion are slightly better with entecavir and tenonfovir. Ninety-six weeks of entecavir results in 5% seroconversion rate and 4 years of tenofovir yields a 10% seroconversion rate. The best HBsAg seroconversion rate (15%) is seen after 72 weeks of treatment with pegylated interferon alfa-2a and lamivudine[10-12]. Although seroconversion of HBsAg doesn't occur frequently, multiple studies show that treatment favorably impacts fibrosis, survival and reduces HCC development in patients who are treated for CHB.

The first nucleoside approved for the treatment of HBV was lamivudine. However, development of resistance with prolonged treatment has limited its use. After 5 years of therapy, resistance is reported to be as high as 75%[13]. Telbivudine and adefovir have a moderate genetic barrier to resistance and are considered to be are second line therapies. Currently, entecavir and

tenofovir are first line agents for treating CHB because they have such a high barrier to resistance. Many studies with nucleos(t)ide therapy have confirmed a decrease in the rate of HCC in treated patients, regardless of the strength of the proposed treatment's barrier to resistance.

TREATMENT OF HBV AND HCC

Antiviral therapy with NAs and interferon can improve liver fibrosis and suppress HBV viral replication, which leads to decreased HCC incidence in patients with CHB[14]. Most of the studies describing the impact of treating CHB on the incidence of liver cancer evaluated the first generation drugs, specifically lamivudine and adefovir. There is less available data regarding the effect of the 3rd generation drugs, tenofovir and entecavir. One recent meta-analysis of patients with HBsAg seroclearance (n = 34,952) showed a significantly decreased risk for developing HCC in comparison to those with who did not seroconvert [risk ratio (RR) 0.34, 95% confidence interval (CI): 0.20-0.56, P < 0.001], but among those who seroconverted, 2.29% (95%CI: 1.19-4.37) still developed HCC[15].

Adefovir and lamivudine

Liaw *et al.*[3] published the only randomized clinical trial that addresses the benefits of using lamivudine in CHB patients with cirrhosis or advanced fibrosis proven by biopsy. Compared to the placebo group, the lamivudine group had a significant reduction in HCC, 7.4% *vs.* 3.9% respectively (HR 0.49, P = 0.047). Additionally, the group treated with lamivudine had a nearly 50% reduction in progression of disease (7.8% *vs.* 17.7%, HR 0.45, P = 0.001). As a result of the significant difference found between the 2 arms, the study was stopped prematurely after a mean duration of 32.4 months.

The advantages of using the first-generation NAs to reduce HCC risk has since been supported in meta-analyses and systematic reviews. In a meta-analysis evaluating 5 studies that compared oral treatment to placebo, treatment with NAs was associated with 78% reduced incidence of HCC (RR 0.22, P < 0.001) irrespective of cirrhosis. Treatment with NAs has also been shown to benefit patients who developed treatment resistance (NA 3.3% *vs.* control 6.4%, RR 0.52, P = 0.04)[16]. Similar results were reported in a systematic review that assesses adefovir, lamivudine, and the combination of both *vs.* placebo in 3,881 CHB patients naive to treatment with NAs. Over a period of 42 months, HCC incidence was lower in treated patients (2.8%) compared to patients who were not treated (6.4%; P = 0.003)[17]. Another meta-analysis reported rates of HCC of 3.5% in lamivudine-treated CHB patients compared to 9.6% in CHB patients who were not treated, over a period of 4 years[18].

Entecavir and tenofovir

The introduction of the third generation NAs, tenofovir and entecavir, which both have a high genetic barrier to resistance, has led to further decreases in HCC incidence. A retrospective study comparing the incidence of HCC in entecavir-treated patients to a historical cohort of lamivudine-treated patients without rescue therapy in the event of resistance development was conducted in Japan. Propensity score matching was used to eliminate baseline differences and the authors found that entecavir-treated patients had a lower 5-year cumulative incidence of HCC compared to historical controls (3.7% *vs.* 13.7%, P < 0.001). The benefit of treatment was seen mainly in cirrhotic patients, 7% in the entecavir group *vs.* 39% in historic controls (P = 0.049) compared to the non-cirrhotic group, and 3.3% in the entecavir *vs.* 3% in controls (P > 0.05)[19]. In an observational study conducted by Wong *et al.*[20], there was also decreased incidence of HCC with entecavir treatment compared to historical controls, also significant only in cirrhotic patients (13.8% *vs.* 26.4%, P = 0.049). A similar observational study by Su *et al.*[21] of patients with cirrhosis demonstrated 5 year cumulative HCC incidence of 26.4% in the untreated historical cohort and 11.3% in the treated cohort with entecavir resulting in reduction of HCC risk by approximately 60% (HR 0.40, 95%CI 0.28-0.57). In another propensity score-matched study of Japanese patients (n = 234), Kumada *et al.*[22] determined that entecavir therapy significantly reduced HCC incidence; the 5- and 10-year cumulative incidence of HCC were 11.3% and 40% in untreated controls, respectively, compared to 2.7% and 3.3% in patients treated with entecavir. Long-term entecavir treatment has been shown to reduce fibrosis by more than 1 point by the Ishak fibrosis score in 88% of patients who were treated for 6 years[23]. A large retrospective study of Taiwanese patients (n = 21,595), assessed a cohort of NA-treated patients and a cohort of patients receiving hepatoprotective agents, but no NA treatment matched by propensity score. The 7-year incidence of HCC was significantly lower in the cohort treated with NA (7.3%), compared to the non-NA treated cohort (22.7%) (adjusted HR 0.37; P < 0.001). In this study, the benefits of NA therapy were noted among patients without (HR 0.27) cirrhosis in addition to patients with cirrhosis (HR 0.72)[24].

A recent retrospective study conducted in Canada utilized the REACH-B scoring system to evaluate the risk of developing HCC among patients treated

with NAs. A total of 322 patients were followed for a median of 3.2 years; median treatment duration with NAs was 3.4 years (interquartile range 1.6-5.9) and 80% of the patients were treated with tenofovir or entecavir. During the study period, 11 patients, 3.2%, developed HCC; 9 of these were Asian men. Cirrhosis was the strongest risk factor for HCC development (unadjusted risk 22-fold); patients with cirrhosis had an annual HCC incidence rate of 4.3% *vs*. 0.2% in patients without cirrhosis. Use of NAs reduced the risk of HCC development; based on the REACH-B model, there was a 50% relative reduction in HCC incidence with NA use, noted as early as 4 years after initiation of treatment[25]. The Chronic Hepatitis Cohort Study, a longitudinal study in the United States, recently evaluated the relationship between CHB therapy and HCC incidence in 2,671 patients. Patients were diagnosed with CHB between 1992 to 2011 and data were analyzed and collected over a 5-year period; 49% of the sample was Asian. Using propensity score matching and Cox regression analysis, the authors found that patients treated with antivirals had a lower risk of HCC than those who were not treated with antivirals (adjusted HR 0.39; 95%CI 0.27-0.56; $P < 0.001$), after adjusting for abnormal level of alanine aminotransferase (ALT). Like the Canadian study above, the observational, retrospective, multicenter cohort study ENUMERATE conducted in the United States used the REACH-B system to assess HCC risk in NA-treated patients. The study included 841 treatment-naïve CHB patients over an 8-year period who had received > 12 months of entacavir with a median follow-up of 4 years. Overall, HCC was diagnosed in 17 patients (2.6%): 8 patients had cirrhosis (13.1%) and developed HCC and 9 patients without cirrhosis (1.5%) developed HCC. In comparison to those who did not develop HCC, the patients with HCC were more likely to have cirrhosis (47.1% *vs*. 8.4%) and to be older (53 years *vs.* 47 years). Among patients who did not have cirrhosis, the observed HCC incidence was lower than the predicted incidence by the fourth year [standardized incidence ratio (SIR) 0.37; 95%CI 0.166-0.82]. By 8.2 years, the maximum follow-up time, the observed incidence of HCC was significantly lower than predicted for all patients (SIR 0.56; 95%CI 0.35-0.905)[26].

In addition to reversing fibrosis, tenofovir therapy has been shown to decrease HCC risk. In the seminal study by Marcellin *et al.*[27], treatment with tenofovir for 5 years led to improvement in histology and regression of fibrosis regression (≥ 1 point decrease by Ishak scoring system) in 87% and 51% of the patients, respectively. Kim *et al.*[28] compared the observed HCC incidence among the 641 patients enrolled in 2 tenofovir registration trials to the incidence of HCC estimated by the REACH-B risk calculator. Starting at 3.3 years, divergence emerged and progressively widened between the predicted and observed incidence of HCC between the 2 groups. Furthermore, at latest follow-up (median of 5.52 years), the SIR between observed and predicted supporting that treatment with tenofovir is beneficial. A recent study conducted in Taiwan examined the efficacy and safety of treatment in NA-naive and NA-experienced patients with CHB; after 3 years of therapy, cumulative HCC incidence at 12, 24 and 36 months were 0%, 1.2%, and 4.8%, respectively, and no significant differences were found between NA-naive and NA-experienced patients in regards to HCC development[29].

IMPACT OF NA CHOICE ON HCC INCIDENCE

In a study conducted in Korea, patients with compensated cirrhosis secondary to CHB, hepatitis B DNA < 2,000 IU/mL, and normal ALT had HCC incidence of nearly 10% over 5 years, but NA therapy reduced incidence to 5.9% for HBV patients treated with NAs; longer duration of treatment and virological response were associated with lower risk of HCC[30]. A recent multicenter study demonstrated a reduction of 77% in HCC incidence in those treated with NAs treatment compared to those who were untreated; this was adjusted for age, gender, ALT, and HBV DNA and was independent of the presence of cirrhosis[31].

Several studies have also evaluated whether the choice of NA affects risk reduction of HCC. In a retrospective study of CHB patients with cirrhosis (n = 227, 104 with decompensated cirrhosis) who were followed over 21-36 months, Koklu *et al.*[32] showed the incidence of HCC to be 3%, 5%, and 8%, respectively, in the tenofovir, entacavir, and lamivudine groups. There was no significant difference found between the NA in the prevention of HCC. In a study of 355 treatment-naïve patients with CHB, 39.2% of whom had cirrhosis, who received entecavir or tenofovir, Idilman *et al.*[33] found that the cumulative incidence of HCC at 1 year was 3.3% and at 4 years was 7.3%. No significant difference was found between the 2 groups. A multicenter European study evaluated 1,756 Caucasian patients in an attempt to evaluate the impact of treatment with entecavir and/or tenofovir for 39 months on HCC occurrence. Overall, the 5-year cumulative probability of HCC was 8.7%. In patients without cirrhosis, the cumulative 5-year HCC rate was 3.7% compared to 17.5% in patients with cirrhosis and 36.3% in patients with decompensated cirrhosis[34]. In a recent review of NAs including lamivudine, tenofovir, and entecavir, Papatheodoridis *et al.*[35] concluded

that no significant difference exists between agents in preventing HCC even in patients who were rescued after development of lamivudine resistance.

A recent Greek analysis compared a cohort of patients treated with entecavir (n = 321), for a median duration of 40 months to a matched cohort of patients (n = 818), initially treated with lamivudine for a median duration of 60 months. Using multivariable Cox regression analysis, risk of HCC was independently associated with male gender (P = 0.011), older age (P < 0.001), and cirrhosis (P = 0.025); HCC risk was not associated with the choice of agent used, at least for the first 5 years[36]. In a Taiwanese population-based cohort study, 1,544 patients with active hepatitis due to HBV taking lamivudine, entecavir, tenofovir, or telbivudine over an 8-year period were evaluated for HCC risk and risk of mortality. For the propensity score matching, patients not treated with NAs (n = 1,544), were selected as the comparison group. As mentioned previously, the treated cohort had a significantly lower rate of HCC occurrence (6.0%; 95%CI 4.4%-7.9%) compared to the cohort not treated with NAs (8.5%; 95%CI 6.6%-10.6%; P = 0.0025). Overall mortality rate for the treated cohort was 6.9% (95%CI 5.3%-8.7%) compared to 9.4% for the untreated cohort (95%CI 7.7%-11.3%) (P = 0.0003). Cox regression analyses demonstrated that use of NAs use significantly reduced the risk of HCC (HR 0.64; 95%CI 0.45-0.93; P = 0.017) and overall mortality (HR 0.58; 95%CI 0.43-0.79; P < 0.001)[37].

Finally, there is new evidence that treatment of CHB reduces mortality related to HCC and HCC recurrence in patients undergoing curative treatments[38]. Huang *et al.*[38] demonstrated antiviral therapy after liver resection to be an independent protective factor of late tumor recurrence (HR 0.348). Similar results were reported by Yin *et al.*[39] In a randomized controlled trial, antiviral therapy reduced both tumor recurrence (HR 0.48) and HCC-related death (0.26). In a study of Taiwanese patients undergoing resection (n = 4,569), those who received NA had significantly lower recurrence rate at 6 years compared to patients not treated with NAs (45.6% *vs.* 54.6% respectively) (P < 0.001). Additionally, the NA-treated group had lower mortality overall at 6 years (29% *vs.* 42.4%) (P < 0.001)[40]. In a recent meta-analysis including 8,204 patients status-post curative resection of HCC, high viral load was significantly associated with increased risk of recurrence, poorer disease-free survival and overall survival of HBV-related HCC after surgical resection. However, NA therapy significantly decreased the recurrence risk (RR 0.69; 95%CI 0.59-0.80; P < 0.001) and improved both disease-free (RR 0.70; 95%CI 0.58-0.83; P < 0.001) and overall survival (RR 0.46; 95%CI 0.32-0.68; P < 0.001) in these patients[41]. Clearly, surgical and medical treatment of CHB improves mortality due to HCC and reduces its recurrence.

LIMITATIONS OF THE HCC PREDICTOR MODELS

Several HCC risk calculators have been proposed including the REACH-B based on a Taiwanese population, the Chinese-University-Hepatocellular carcinoma score (CU-HCC) score[42], and the GAG-HCC score, which incorporates age, gender, HBV DNA, presence of core promoter mutations and cirrhosis[43]. These models were developed in Asians and the application to other populations is unclear, though one study showed good performance in non-Asians[44]. The platelet, age, gender (PAGE-B score is based on platelet, age and gender and was developed to assess risk of HCC in Caucasians. Another limitation of these models is that they do not include a liver fibrosis assessment such as transient elastography. In addition, some models like the CU-HCC included 15% of HBV treated patients rather than all treatment naïve patients. It is questionable whether the HCC risk predictor models can be used in patients on HBV therapy, as therapy leads to viral suppression and may lead to fibrosis regression. In addition, the absence of the degree of HBV viral suppression in some models is a major limitation of the risk calculators[35].

CONCLUSION

In patients with CHB, successful treatment can reduce but not eliminate the risk of developing HCC, regardless of the presence or absence of cirrhosis. Treatment of CHB can reverse fibrosis as demonstrated by studies involving the third-generation NAs tenofovir and entecavir, which have a high genetic barrier to resistance. Additionally, growing evidence supports that treatment of CHB reduces recurrence rates of HCC and HCC-related mortality in CHB patients who received curative treatments for HCC.

Most data regarding chemoprevention is derived from studies using lamivudine and this significantly limits interpretation of the data. It is possible that the chemopreventative effect is more pronounced with the long term use of entecavir and tenofovir, which have a much lower risk of resistance with prolonged use when compared to lamivudine. Most of the studies evaluating the effect of chemoprevention are retrospective in nature, which is another major limitation. In other

studies, the reduction of HCC incidence was not the primary outcome measured. Despite these limitations, results from medium-length follow up studies with entecavir and tenofovir and analyses of registration trials already suggest that treatment with these NAs have chemopreventive effects and reduce risk of HCC.

Continued viral suppression is critical to minimize the risk of HCC development, although achieving viral suppression will not eliminate the risk of HCC, specifically in high-risk patients with advanced fibrosis or cirrhosis. In these situations, continuous surveillance for HCC is essential. Prospective studies which address the confounding factors such as gender, age, fibrosis stage. Finally, HCC screening algorithms are necessary to better elucidate the impact of chemoprevention on HCC development in HBV patients treated with the newer nucleos(t)ide agents.

In summary, treatment of hepatitis B leads to decreased incidence of hepatocellular carcinoma in Asians and Caucasians regardless of the nucleos(t)ide used. Also, decreasing the HBV viral load, regardless of achieving seroconversion, results in decreased HCC incidence. Despite this reduction in HCC incidence, patients treated with nucleos(t)ides still need to undergo liver cancer screening. Several HCC predictor models have been developed, but as of now, there are limitations in applicability.

DECLARATIONS

Authors' contributions

Project conception: W.S. Ayoub, P. Martin, P.D. Jones
Literature review, manuscript drafting and critical revision: W.S. Ayoub, F. Dailey, P. Martin, P.D. Jones

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Conflicts of interest

Walid S. Ayoub, Francis Dailey, Paul Martin, Patricia D. Jones declare that they have no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

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