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Optimize nucleot(s)ide analogues' to prevent hepatocellular carcinoma in patients with chronic hepatitis B: a lesson from real-world evidence

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Abstract

The goal of antiviral treatment for chronic hepatitis B (CHB) is to reduce the risk of liver-related complications, including liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). It is not possible to eliminate hepatitis B virus from the host with currently available antiviral treatments; hence, a realistic goal is to decrease the risk of HCC as much as possible with an appropriate and timely antiviral treatment. For the past decades, real-world evidence has enlarged the field of CHB research. Presently, there is mounting evidence that randomized clinical trials are not technically and ethically possible to conduct. In this review, we focus on secondary prevention by antiviral treatment in patients with CHB, mainly based on real-world evidence.

Keywords: Hepatitis B virus, hepatocellular carcinoma, antiviral agent

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem that causes life-threatening liver diseases, including hepatocellular carcinoma (HCC), cirrhosis, and end-stage liver disease. Globally, 292 million people are infected with HBV, and about 1.0 million people die annually from HBV-related

liver diseases, with an increasing trend[1,2]. Moreover, HBV infection causes more than 50% of HCC cases worldwide[3]. The incidence of HBV-associated HCC varies geographically, depending on regional exposure to risk factors and the availability of healthcare resources[2,4]. Most HCC cases occur in East Asia and sub-Saharan Africa, where viral hepatitis is an endemic[5]. The prevalence of HBV infection has been decreasing since the successful introduction of HBV vaccination programs, which are the primary prevention methods for HCC. However, in many countries, the overall clinical burden of HCC is still growing.

Three preventive measures may reduce HBV-related HCC development. Primary preventions may be achieved by vaccination, change in behavioral patterns, and prevention of mother-to-child-transmission. Secondary prevention includes effective antiviral treatment against the development of HBV-related HCC and surveillance measures to detect early stage of HCC in those infected by HBV. Tertiary prevention is an effort to reduce the recurrence of HBV-related HCC in patients who have been successfully treated for HCC.

Currently, in the field of chronic hepatitis B (CHB), there is much interest in real-world evidence (RWE) that complements the knowledge gained from traditional clinical trials and provides important information about uncommon events, long-term clinical outcomes such as HCC, comparative treatment effectiveness, disease burden, and many more topics. For the past decade, progress in research design and advancements in statistical methodology have allowed the widespread adoption of RWE in clinical CHB research.

In this context, the aims of the present review are to (1) outline the secondary prevention of HBV-related HCC by nucleos(t)ide analogues (NUCs), with a specific focus on RWE; and (2) suggest possible strategies to further reduce the risk of HCC in patients with CHB.

HEPATOCELLULAR CARCINOMA DEVELOPMENT IN PATIENTS WITH CHRONIC HEPATITIS B

HBV contributes to hepatocarcinogenesis via three mechanisms. The first involves chronic inflammation and hepatocyte regeneration due to persistent and sustained HBV replication. During this repetitive process, DNA mutation causes carcinogenesis[6]. Persistent and uncontrolled HBV replication is associated with an increased risk of HCC. One large-scale, untreated cohort study of more than 3,000 patients with CHB clearly showed a dose - response relationship between the serum HBV DNA level and the incremental risk of HCC[7]. In a long-term follow-up of the same cohort, persistently high viral load was associated with a higher rate of HCC than sustained low viral load[8]. Another study showed that serum hepatitis B surface antigen (HBsAg) level was also associated with HCC risk, especially in patients with low level viremia (HBV DNA < 2000 IU/mL)[9]. In this regard, antiviral treatment to decrease the development of HBV-associated HCC mainly focuses on reducing the level of HBV DNA, which is a primary function of NUCs [Table 1]. The second mechanism involves chromosomal instability, whereby part of the HBV genome becomes integrated into the host hepatocyte genome, resulting in host DNA[10]. This mechanism of hepatocarcinogenesis can lead to HBV-associated HCC in patients with CHB who have no cirrhosis. Indeed, patients with occult hepatitis B infection (OBI) still carry the risk of HCC by this mechanism despite a negative serum HBsAg profile[11,12]. Therefore, the risk of HCC is not completely eliminated despite remarkable advances in antiviral treatment.

Liver cirrhosis itself is well known as a strong risk factor for HCC, and is characterized by tissue fibrosis and the conversion of normal liver architecture into structurally abnormal nodules[13]. If cirrhosis, regardless of etiology, is established, then the risk of HCC remains despite an effective antiviral treatment. Indeed, HBV-related HCC risk reduction by long-term antiviral treatment is more pronounced in patients without cirrhosis[14]. Several mechanisms have been postulated that induce hepatocarcinogenesis from cirrhotic liver, including telomere dysfunction, impaired hepatocyte proliferation by loss of replicative competition, and promoting tumor cell proliferation by an altered milieu[15].

Table 1. Summary of real-world evidence regarding the risk of hepatocellular carcinoma in chronic hepatitis B patients treated with nucleos(t)ide analogues

Ref.	Data source, country	No. of Patients (Male)	Age, years[a]	No. (%) of HBeAg (+)	No. (%) of liver cirrhosis	Follow-up time	Main findings
Wu *et al.*[8] (2007)	Taiwan 1989-1992	1143 (1143) HCC 112 (112) No HCC 1031 (1031)	Age at onset HCC (59.2, 39.8-78.7) No HCC (-)	HCC 17 (15.5) No HCC 92 (9.1)	HCC 66 (58.9) No HCC NA	HCC 7.3 (5 0.6-15.0) years No HCC 13.4 (5 2.1-16.0) years	(Entire cohort) HCC, HBV DNA ≥ 4.39 log copies/ml *vs.* sustained low viral load; OR: 5.04; 95%CI: 2.31-11.00 HCC, ALT elevation *vs.* normal level; OR: 2.84; 95%CI: 1.46-5.51 HCC, HBV genotype C *vs.* B or B + C; OR: 5.97; 95%CI: 3.44-10.34 HCC, HBeAg positive *vs.* negative; OR: 0.89; 95%CI: 0.40-1.94
Tseng *et al.*[9] (2012)	Taiwan 1985-1995	2688 (1634)	28-39; 1407 (52.3) 40-49; 763 (28.4) 50-59; 369 (13.7) ≥ 60; 149 (5.5)	523 (24.2)	0 (0)	14.7 ± 4.3	(Entire cohort) Predicting 10-year HCC, HBV DNA; ROC, 0.70; 95%CI: 0.65-0.75 Predicting 10-year HCC, ALT; ROC, 0.75; 95%CI: 0.70-0.79 Predicting 10-year HCC, HBsAg; ROC, 0.58; 95%CI: 0.52-0.64 (HBeAg negative with low viral load cohort) HCC, HBsAg level < 1000 IU/mL *vs.* ≥ 1000, HR: 13.7; 95%CI: 4.8-39.3)
Hosaka *et al.*[30] (2012)	Japan 2004-2010	(Entire cohort) 1615 (1035) Entecavir 472 (315) Control 1143 (720) (PS matched cohort) ETV 316 (210) Control 316 (210)	(Entire cohort) 42 (13.5) ETV 47 (12.4) Control 39 (13.1) (PS matched cohort) ETV 3.3 (2.3-4.3) Control 7.6 (3.4-13.7)	(Entire cohort) 617 (38) ETV 219 (46) Control 398 (35) (PS matched cohort) ETV 135 (43) Control 133 (42)	(Entire cohort) 311 (19) ETV 116 (25) Control 195 (17) (PS matched cohort) ETV 79 (25) Control 85 (29)	(Entire cohort) 5.4 (3.1-13.2) ETV 3.2 (2.1-4.3) Control 9.5 (4.4-16.1) (PS matched cohort) ETV 3.3 (2.3-4.3) Control 7.6 (3.4-13.7)	(PS matched cohort) HCC, Age (per year); HR: 1.06; 95%CI: 1.03-1.09 HCC, Cirrhosis; HR: 4.28; 95%CI: 1.88-9.73 HCC, HBeAg positivity; HR: 2.26; 95%CI: 1.18-4.34 HCC, low platelet; HR: 5.64; 95%CI: 2.13-15.0 HCC, ETV *vs.* Control; HR: 0.37; 95%CI: 0.15-0.91
Wong *et al.*[31] (2013)	Hong Kong 2005-2012	(Entire cohort) ETV 1466 (1049) Control 424 (276) (Without cirrhosis cohort) ETV 984 (693) Control 55 (221) (With cirrhosis cohort) ETV 482 (356) Control 69 (55)	(Entire cohort) ETV 51 ± 12 Control 41 ± 33 (Without cirrhosis cohort) ETV 49 ± 12 Control 39 ± 13 (With cirrhosis cohort) ETV 55 ± 11 Control 51 ± 11	(Entire cohort) ETV 443 (30) Control 155 (37) (Without cirrhosis cohort) ETV 397(31) Control 136(38) (With cirrhosis cohort) ETV 136 (28) Control 19 (28)	(Entire cohort) ETV 482 (33) Control 69 (16) (Without cirrhosis cohort) ETV 0 (0) Control 0 (0) (With cirrhosis cohort) ETV 482 (100) Control 69 (100)	(Entire cohort) ETV 36 ± 13 months Control 114 ± 31	(Without cirrhosis cohort) The 3-year HCC incidence; ETV *vs.* control; 1.4% (95%CI: 1.0-1.8) *vs.* 1.7% (95%CI: 1.0-2.4) The 5-year HCC incidence; ETV *vs.* control; 3.3% (95%CI: 1.3-5.3) *vs.* 3.0% (95%CI: 2.1-3.9) (With cirrhosis cohort) The 3-year HCC incidence; ETV *vs.* control; 9.1% (95%CI: 7.6-10.6) *vs.* 14.5% (95%CI: 11.0-18.0); *P* = 0.04 The 5-year HCC incidence; ETV *vs.* control; 13.8% (95%CI: 11.3-16.3) *vs.* 26.4% (95%CI: 20.7-32.1); *P* = 0.036

Su *et al.*[32] (2016)	Taiwan 2008	1818 (1348) ETV 1315 (963) Untreated 503 (385)	ETV 55 (47-62) Untreated 50 (42-59)	ETV 385 (29.3) Untreated 149 (29.6)	ETV 1315 (100) Untreated 503 (100)	ETV 4 years (5255 PYs) Untreated 6 years (3416 PYs)	(Entire cohort) HCC incidence, ETV *vs.* control during study peroid; (119/1315) *vs.* (121/503) The 4- year HCC incidence; ETV *vs.* control; 9.4% (95%CI: 7.8-11.3) *vs.* 17.5% (95%CI: 14.3-21.3) HCC, ETV *vs.* control; HR: 0.40; 95%CI: 0.28-0.57 (ETV cohort) HCC, older age; HR: 1.06; 95%CI: 1.04-1.08 HCC, male gender; HR: 1.88; 95%CI: 1.20-2.96 HCC, HBeAg positivity; HR: 1.89; 95%CI: 1.23-2.92 HCC, baseline AFP level ≥ 7 ng/mL; HR: 1.93; 95%CI: 1.30-2.88 HCC, 1- year virological response; HR: 0.62; 95%CI: 0.40-0.98
Kim *et al.*[14] (2015)	Multinational 2005-2006	641 (468) Cirrhosis 152 (123) Without cirrhosis 482 (345)	Cirrhosis 45.2 (10.6) Without cirrhosis 38.4 (11.8)	Cirrhosis 60 (39) Without cirrhosis 199 (41)	NA	Cirrhosis 7.36 years (range, 0.08-7.43 years) Without cirrhosis 7.36 years (range, 0.00-7.55 years)	(Entire cohort) Overall HCC incidence, 0.37% per year; 95%CI: 0.20-0.62 (Cirrhosis cohort) Overall HCC incidence, 0.65% per year; 95%CI: 0.24-1.40 HCC, SIR; 0.51; 95%CI: 0.231-1.144 (Without cirrhosis cohort) Overall HCC incidence, 0.28% per year; 95%CI: 0.12-0.56 HCC, SIR; 0.40; 95%CI: 0.199-0.795
Liu *et al.*[33] (2019)	Multinational 1997-2017	1088 (778) Untreated 291 (227) TDF 797 (551)	Untreated 48 (44-56) TDF 53 (47-58)	Untreated 69 (23.8) TDF 356 (44.7)	Untreated 291 (100) TDF 797 (100)	Untreated 121 (70-181) months TDF 56 (46-62) months	The 3-year HCC incidence; Untreated *vs.* TDF; 7.4% *vs.* 5.5%; $P = 0.64$ The 5-year HCC incidence; Untreated *vs.* TDF; 14.9% *vs.* 9.8%, $P = 0.07$ HCC, TDF; HR: 0.46; 95%CI: 0.29-0.75; $P < 0.01$ HCC, Albumin; HR: 0.93; 95%CI: 0.90-0.97; $P < 0.01$
Papatheodoridis *et al.*[34] (2017)	Europe 2012	1951 (1379) Within 5 years follow up 749 (524) Beyond 5 years follow up 1205 (855)	53 ± 14 Within 5 years follow up 54 ± 14 Beyond 5 years follow up 52 ± 13	348 (18) Within 5 years follow up 116 (16) Beyond 5 years follow up 232 (19)	526 (27) Within 5 years follow up 201 (27) Beyond 5 years follow up 325 (27)	72 (35) Within 5 years follow up 42 (28) Beyond 5 years follow up 82 (18)	(Entire cohort) Yearly HCC incidence; within 5 years *vs.* 5-10 years; 1.22% *vs.* 0.73%; $P = 0.050$ (Cirrhosis cohort) Yearly HCC incidence; within 5 years *vs.* 5-10 years; 3.22% *vs.* 1.57%, $P = 0.039$ (Beyond 5 years of HCC) HCC, older age; HR: 1.06; 95%CI: 1.01-1.11; $P = 0.032$ HCC, lower platelets at baseline; HR: 0.99; 95%CI: 0.98-1.00, $P = 0.021$ HCC, liver stiffness ≥ 12 kPa at 5 year ; HR: 4.10; 95%CI: 1.10-15.33, $P = 0.036$

Lim *et al.*[36] (2014)	Korea 1999-2011	(Entire cohort) ETV 2000 (1288) LMV 3374 (2386) (PS matched overall cohort) ETV 1792 (1193) LMV 1792 (1179)	(Entire cohort) ETV 47 ± 11 LMV 43 ± 11 (PS matched overall cohort) ETV 46.1 ± 10.1 LMV 46.1 ± 10.9	(Entire cohort) ETV 47 ± 11 LMV 43 ± 11 (PS matched overall cohort) ETV 1133 (63.2%) LMV 1107 (61.8%)	(Entire cohort) ETV 1071 (53.6%) LMV 1621 (48.0%) (PS matched overall cohort) ETV 933 (52.1%) LMV 934 (52.1%)	(Entire cohort) ETV 3.1 (2.2-4.3) LMV 8.7 (6.5-11.5)	(Entire cohort) HCC, HR; ETV *vs.* LMV; HR: 1.08; 95%CI: 0.87-1.34 (Overall PS matched cohort) HCC, HR; ETV *vs.* LMV; HR: 1.01; 95%CI: 0.80-1.27 (PS matched non-cirrhosis cohort) HCC, HR; ETV *vs.* LMV; HR: 1.26; 95%CI: 0.68-2.34 (PS matched cirrhosis cohort) HCC, HR; ETV *vs.* LMV; HR: 1.00; 95%CI: 0.78-1.28
Kim *et al.*[37] (2016)	Korea 2006-2013	(Entire) LMV 435 (301) ETV 644 (395) (PS matched model 1) LMV 342 (214) ETV 342 (224) (PS matched 2) LMV 338 (219) ETV 338 (225)	(Entire) LMV 47 (39-54) ETV 50 (43-56) (PS matched 1) LMV 49 (41-56) ETV 49 (41-55) (PS matched 4) LMV 48 (41-55) ETV 49 (42-55)	(Entire) LMV 231 (53.1) ETV 339 (52.6) (PS matched 1) LMV 178 (52.0) ETV 188 (55.0) (PS matched 6) LMV 179 (53.0) ETV 177 (52.4)	(Entire) LMV 175 (40.2) ETV 367 (57.0) (PS matched 1) LMV 153 (44.7) ETV 187 (54.7) (PS matched 2) LMV 166 (49.1) ETV 160 (47.3)	NA	(Entire cohort) The 7-year HCC incidence; LMV *vs.* ETV; 10.2% *vs.* 13.4%; *P* = 0.107 HCC, Liver stiffness; HR: 1.02; 95%CI: 1.00-1.03; *P* = 0.035 (PSM 1) The 7-year HCC incidence; LMV *vs.* ETV;10.5% *vs.* 9.9%; *P* = 0.873 (PSM 2) The 7-year HCC incidence; LMV *vs.* ETV; 11.9% *vs.* 12.6%; *P* = 0.648
Lampertico *et al.*[43] (2020)	Europe 2012	1935 (1365) ETV: 772 (538) TDF: 1163 (827)	ETV: 52 ± 14 TDF: 53 ± 13	ETV: 110 (14.2) TDF: 233 (20.0)	ETV: 166 (21.5) TDF: 358 (30.8)	7.6 (5.0-9.6) years ETV: 7.6 (4.3-9.5) years TDF: 7.5 (5.4-9.6) years	(Entire cohort) The 5-year HCC incidence: ETV *vs.* TDF; 5.4% *vs.* 6.4%; *P* = 0.321
Shin *et al.*[51] (2018)	Korea 2000-2013	1910 (1249) IT: 413 (276) IA: 1497 (973)	IT: 38 ± 11 IA: 40 ± 11	1910 (100)	0 (0)	IT: 4.9 (2.4-8.6) IA: 6.7 (3.7-10.3)	(Entire cohort) HCC, IA *vs.* IT; HR: 2.54; 95%CI: 1.54-4.18 Death/transplant, IA *vs.* IT; HR: 3.38; 95%CI: 1.85-6.16
Chang *et al.*[61] (2017)	Korea 2006-2016	484 (241) Treatment: 397 (195) Untreated: 87 (46)	Treatment: 41.5 ± 12.5 Untreated: 43.2 ± 13.0	484 (100)	0 (0)	66.5 (23-80) Untreated: 71 (24-82) Treated: 50 (42-66)	(PSM cohort) HCC, Treated *vs.* untreated; HR: 0.234; 95%CI: 0.050-1.104 (IPTW cohort) HCC, Treated *vs.* untreated; HR: 0.189; 95%CI: 0.052-0.692
Choi *et al.*[62] (2019)	Korea 2000-2013	5414 (3024) Inactive: 3572 (1930) Replicative: 900 (473) Mildly active: 396 (305) Active: 546 (316)	47 Inactive: 47 ± 11 Replicative: 47 ± 11 Mildly active: 46 ± 10 Active: 47 ± 9	0 (0)	0 (0)	median 8.9 Inactive: 9.9 (6.3-13.1) Replicative: 7.8 (5.3-9.2) Mildly active: 8.2 (6.0-11.2) Active: 7.9 (5.7-10.6)	(PSM cohort) HCC, Active treated *vs.* Untreated replicative; HR: 1.76; 95%CI: 1.00-3.10

ETV: Entecavir; HCC: hepatocellular carcinoma; HR: hazard ratio; IA: immune-active; IT: immune-tolerant; LMV: lamivudine; NA: not available; SIR: standardized incidence ratio; PSM: propensity-score matching; TDF: tenofovir disoproxil fumarate.

CHEMOPREVENTION OF HCC BY INTERFERON AND NUCS

Currently available antiviral treatments for CHB include interferon-α and NUCs. Interferon has been widely used as an antiviral treatment for many decades until orally available NUCs were introduced. Interferon-based antiviral treatment needs finite duration of treatment resulting in durable host immune control over HBV. Randomized trials and meta-analysis have demonstrated that interferon-based treatment reduces the risk of HCC by 40%-50% in treated compared to untreated patients[16-19]. Although interferons reduce the risk of HCC, their detailed usage and mechanisms are beyond the scope of this review. NUCs are an oral antiviral treatment; seven are currently available, namely, lamivudine, adefovir, telbivudine, entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide, and besifovir. According to the international treatment guidelines for CHB, ETV, TDF, and tenofovir alafenamide are equally recommended as the preferred agents for treating CHB[20-22].

Chemopreventive effects of various NUCs from previous studies are summarized in Table 1. Lamivudine, the first available NUC, showed a protective effect against HCC development in a randomized study with a hazard ratio (HR) of 0.49[23]. This study is the only randomized, placebo-controlled trial comparing HCC prevention by an NUC and a placebo. Subsequent studies also show that lamivudine significantly reduces the risk of HCC in patients with CHB[24-26]. Two meta-analyses have indicated that treatment with NUCs reduced the risk of HBV-associated HCC by 74%-78% compared with treatment without NUCs[27,28]. However, the risk of HCC remained higher in patients with resistance-related virological breakthrough than in those with sustained virological response[29], implying that sustained and uncontrolled HBV replication may not reduce the risk of HCC, even under NUC treatment.

Compared with the older generation of NUCs that includes lamivudine, adefovir, and telbivudine, ETV shows greater efficacy because it has a higher genetic barrier to viral resistance. Thus, ETV has begun to replace the old generation of NUCs among patients with resistant HBV and is recommended as a first-line antiviral treatment by the international guidelines since late 2000. A propensity score (PS)-matching study from Japan reported that patients with CHB who were treated with ETV showed a lower risk of 5-year cumulative HCC (3.7%) than an untreated historical cohort (13.7%; $P < 0.001$)[30]. In a cohort study involving 1980 patients with cirrhosis, treatment with ETV reduced the risk of HCC compared with controls (HR = 0.55)[31]. A Taiwanese multicenter study found that ETV treatment in patients with cirrhosis was associated with a 60% reduction in HCC risk compared with a cirrhotic control group[32]. TDF has been widely available since early 2010. In a simulation study, TDF was associated with a reduced incidence of HCC in patients without cirrhosis compared with untreated patients, showing a 60% reduction after 5 years of TDF treatment[14]. A multicenter international retrospective study also revealed that 5 years of TDF treatment reduced the risk of HCC in patients with CHB who had cirrhosis, compared with untreated patients[33]. A long-term follow-up study of Caucasian patients with CHB reported that treatment using either ETV or TDF significantly reduced the risk of HCC[34]. A recent meta-analysis involving 23 observational studies with 59,201 patients in the immune-active phase of infection showed that antiviral treatment decreased the risk of HCC compared with controls, with a HR of 0.5. The same study also analyzed 10 observational studies involving patients with cirrhosis and found that antiviral treatment reduced the risk of HCC, with a HR of 0.6[35].

CONTROVERSIES OVER THE EFFICACY OF HCC RISK REDUCTION AMONG NUC TYPES

Although ETV shows better efficacy in suppressing HBV DNA than old-generation NUCs, the HCC risk reduction is poorer than expected. The aforementioned Japanese study revealed that ETV treatment is associated with a significantly lower risk of HCC than treatment with lamivudine ($P = 0.043$)[30]. However, a large-scale retrospective study of 5,374 patients with CHB treated using either ETV or lamivudine demonstrated that ETV treatment conferred no lower risk of HCC than lamivudine (HR = 1.08, $P = 0.48$)[36].

Another retrospective study used PS-matching analysis and showed similar risk for HCC between the two NUCs[37].

A nationwide Korean cohort study by our group reported that patients with CHB who were treated using TDF had a significantly lower risk of HCC than those treated with ETV[38]. Many subsequent studies reported controversial findings[39-43]. A large-scale cohort study of 29,350 patients with CHB from Hong Kong demonstrated that TDF was associated with a lower risk of HCC than ETV, which was consistent with the nationwide Korean cohort study[40]. In contrast, a multicenter retrospective study from Korea showed no difference in the risk of HCC between these two NUCs[41], and a multinational study also failed to show any significant difference in risk of HCC between ETV and TDF[42]. Recently, our group conducted a meta-analysis comparing the preventive effect against HCC between these two NUCs[44]. We included 15 studies comprising 61,787 patients with CHB who were treated using either ETV or TDF. The results suggested that TDF was associated with a significantly lower risk of HCC than ETV (HR = 0.80, P = 0.003)[44]. Even meta-analyses have presented controversial findings, depending on the characteristics of the included studies, ethnicity, and inclusion of decompensated cirrhosis[45-48]. Notably, our group recently used PS-matching to demonstrate that TDF was associated with significantly higher recurrence-free and overall survival rates than ETV in patients who had undergone curative-intent hepatectomy for HBV-associated HCC[49]. Collectively, most studies have either revealed that there is no difference in risk between the two treatments, or that TDF is associated with a lower risk of HCC[50]. No studies have favored ETV treatment over TDF in regards to HCC risk reduction. This controversy will likely remain unresolved until a randomized controlled trial is performed. However, it is unlikely that any such trial will be carried out, because HCC has a low occurrence, and any plausible trial would require a long-term observational period and a large number of patients[50].

ADHERENCE AND DURATION OF TREATMENT INFLUENCE NUC'S CHEMOPREVENTIVE EFFECTS

Other factors affecting HCC prevention by NUCs include treatment adherence and duration. A study of 894 patients with CHB who were treated with ETV reported that poor adherence, defined as < 90% compliance, was associated with a higher mortality and greater risk of HCC, particularly among patients with cirrhosis[51]. Interestingly, the same group also reported that low levels of HBV DNA, despite the ETV treatment, were not predictive of HCC if patients showed good adherence to ETV treatment. This result emphasized the importance of drug compliance[52]. A nationwide Korean cohort study indicated that the incidence of HCC was incremental in a dose-dependent manner among poor-, intermediate-, and good-adherence groups, although the difference was not significant after multivariable adjustments[53].

The treatment duration of NUCs for chemoprevention of HCC follows the treatment guidelines of CHB[20-22]. Currently, the realistic goal of CHB treatment is a so-called "functional cure", defined as the loss of HBsAg, regardless of HBsAb appearance. Therefore, once NUCs are started, treatment should be continued until this goal is achieved, even though controversies exist. A retrospective study involving 1,951 Caucasian patients with CHB demonstrated that the risk of HCC decreased after the first 5 years of ETV or TDF treatment[34]. However, a Korean retrospective study showed that the incidence of HCC did not significantly differ before and after 5 years of ETV treatment, suggesting that the lon-term risk of HCC in Asian patients with CHB may continue to persist[54]. This issue should be further validated and different NUCs must be compared to infer more conclusively.

WHO SHOULD BE TREATED WITH NUCS TO REDUCE THE RISK OF HCC?

The natural course of CHB is generally classified into four different phases based on serum HBV replicative status, with serum alanine aminotransferase (ALT) level used as a surrogate marker for significant liver

inflammation. These phases include immune-tolerant, immune-active, inactive carrier, and hepatitis B e-antigen (HBeAg)-negative hepatitis. Current international treatment guidelines for CHB universally recommend antiviral treatment in patients with immune-active phase or HbeAg-negative hepatitis[20-22]. Moreover, patients with cirrhosis are advised to initiate antiviral treatment, regardless of serum HBV DNA level[20-22]. Most patients with CHB at a given time can be classified into one phase of the natural CHB course. However, CHB is a dynamic disease that interacts with HBV and host immunity. Hence, the phases of CHB change based on patient age, immunity, and viral replication status. In practice, a few patients with CHB, especially those without cirrhosis, reside in the so called "gray zone", which is not addressed in treatment guidelines. Current international treatment guidelines state that NUC should be initiated based on two main factors: serum HBV DNA and ALT level. Without evidence of cirrhosis, NUC should be started if the serum HBV DNA level is high (≥ 20,000 IU/mL for HBeAg-positive patients and ≥ 2,000 IU/mL for HBeAg-negative patients) or if ALT levels are abnormal [2× the upper limit of normal (ULN)]. However, current treatment criteria leave several unresolved questions. Specifically, are patients with CHB who do not meet the treatment initiation criteria definitely safe from developing HCC without the antiviral treatment? Current treatment initiation criteria stipulate that elevated serum ALT can be used as a surrogate marker of active liver inflammation because liver biopsy is not generally conducted for this purpose. However, mounting evidence indicates that serum ALT levels may not be a good criterion for deciding the initiation of antiviral treatment because it is altered under other non-HBV conditions, such as combined fatty liver disease and heavy alcohol assumption. In addition, previous studies have shown a poor association between serum ALT levels and the degree of necroinflammation in the hepatocytes of biopsied specimens, especially when serum ALT level is only slightly elevated (ALT < 2× ULN)[55,56]. In other words, the current treatment initiation criteria may delay antiviral treatment until significant active liver disease becomes apparent. This assumes that HBV infection is basically harmless in HBV carriers until many decades have passed and only when active liver disease is present[57]. Traditionally, the immune-tolerant phase refers to the immunologically and histologically dormant stage not requiring antiviral treatment, according to the treatment guidelines. In this regard, recent immunological studies have revealed that patients in the immune-tolerant and immune-active phases show a similar HBV-specific T-cell response, indicating that the immune-tolerant phase should not be considered completely benign, as previously assumed[58]. Another study suggested that hepatocarcinogenic processes, such as HBV DNA integration and clonal hepatocyte expansion, were already present during the early phase of CHB, whereas traditional concepts understand the immune-tolerant phase as benign[59]. Indeed, these *in vitro* studies were supported by RWE. A large-scale retrospective study from Korea demonstrated that untreated patients in the immune-tolerant phase had a higher risk of HCC than treated immune-active patients[60]. Another multicenter retrospective study from Korea showed that NUC treatment of patients currently in the immune-tolerant phase reduces the risk of HCC, even if the serum ALT level is below the upper limit of normal[61]. Another gray zone includes patients who are HBeAg-negative and have a high viral load, but have normal or slightly above normal ALT levels. As mentioned above, current treatment guidelines allow treatment initiation if the serum ALT level is more than 2× ULN. However, a retrospective study suggested that untreated HBeAg-negative, high viral-load patients without significant ALT elevation carried a higher risk of HCC than treated active phase patients with elevated serum ALT[62]. The degree of liver fibrosis resulting from hepatocyte injury by necroinflammation is also associated with the development of HCC. To measure the degree of liver fibrosis, liver biopsy has traditionally been used. However, the clinical utility of liver biopsy is limited by its invasiveness, sampling variability, and inter-observer variability. Therefore, several non-invasive tests of fibrosis have been developed and validated[63-65]. These non-invasive assessments of liver fibrosis can aid the treatment decision-making process if a patient does not meet the traditional treatment criteria. Indeed, international guidelines recommend treatment initiation in patients with significant fibrosis by non-invasive assessments[20-22]. Liver biopsy should be preserved in selected cases where serologic and non-invasive tests are inconclusive in determining the disease activity. In addition,

patients with first-degree family history of HCC, extrahepatic manifestations, or age > 40 years may be considered for treatments with antiviral agents considering their increased risk of HCC[66].

Taken together, to prevent HBV-related HCC by using appropriate and timely antiviral treatment, the current treatment initiation criteria might be inadequate and could be expanded based on serum HBV DNA and ALT levels, degree of liver fibrosis, and personal characteristics[57]. Lastly, antiviral treatment is not recommended for patients with OBI by current international guidelines. Unlike overt HBV infection, patients with OBI are HBsAg negate but may have intermittent very low level of serum HBV DNA[11,12]. Indeed, patients with OBI still carry the risk of HCC and the risk of HCC may increase with combined known liver diseases such as chronic HCV infection. However, this area should be further investigated by future studies.

OTHER CONSIDERATIONS WITH NUC TREATMENT TO REDUCE HCC RISK

Many preventive interventions have been carried out in patients with CHB to lower the risk of HCC development, such as lifestyle modification and correct dietary habits[67].

Alcohol

Alcohol consumption is an independent risk factor for HCC, and when patients with CHB drink alcohol, poorer outcomes are expected. The mechanisms of how alcohol interacts with HBV are not fully demonstrated, but it may accelerate viral replication, causing oxidative stress, or hinder the immune system[68]. Heavy alcohol consumption increases HCC risk significantly. A retrospective study in Taiwan compared alcoholic patients with CHB, non-alcoholic patients with CHB, and alcoholic patients. The results of a 10-year cumulative HCC incidence in these groups were 52.8%, 39.8%, and 25.6%, respectively ($P < 0.001$)[69]. In addition, alcohol consumption negatively affects the protective effect of NUCs on HCC. Cumulative alcohol consumption of more than 200 kg for a lifetime was posed as an independent risk factor for HCC in NUC-treated patients with CHB (HR = 2.21, $P = 0.013$)[30].

Smoking

Smoking also confers an increased risk of HCC. According to a study in a European cohort, smoking, even former smoking, was highly related to HCC occurrence in patients with chronic viral hepatitis [former smoking, odds ratio (OR): 1.98, $P = 0.092$; current smoking, OR: 4.55, $P = 0.001$][70]. Smoking also increases the risk of HCC-related mortality. Subjects who were free of malignancy were followed up until the end of the study period or death from HCC. The relative risk of HCC-related mortality was 1.4 in men and 1.1 in women[71].

Metabolic syndrome

Fatty liver disease a crucial factor in HCC. Non-alcoholic fatty liver disease (NAFLD) is closely associated with diabetes, hyperlipidemia, and obesity. Diabetes is also associated with a two-fold increased risk of HCC[72]. Obese patients with CHB are more likely to have HCC. A prospective study was carried out in Taiwan in which 2,903 HBsAg-positive male patients were followed up for 14.7 years[73]. As body mass index (BMI) increased, so did the risk of HCC. Compared with normal-weighted patients (BMI = 18.5-24.9 kg/m^2), overweight patients (BMI = 25.0-29.9 kg/m^2) and obese patients (BMI > 30.0 kg/m^2) were more likely to be suffering from HCC or liver-related death, with HRs of 1.48 and 1.96, respectively[73]. To date, a specific diet affecting the clinical course of CHB is not identified. However, lifestyle modification with a healthy diet and proper exercise is important.

CONCLUSION

Recently, dramatic advancements have been made in HBV treatment; the development of an HBV vaccine and antiviral agents against HBV have tremendously improved clinical outcomes, including viral

hepatitis and its fatal complications. Nevertheless, given the enormous clinical and socio-economical burdens of HCC caused by HBV, CHB should be properly managed with appropriate and timely use of antiviral treatments for secondary prevention. Unfortunately, no current drug can eliminate HBV nor can it completely eliminate the risk of HCC. However, many recent RWEs have provided important insights into secondary prevention of HCC, making clinicians reconsider the indications for antiviral treatment beyond the current treatment guidelines set forth for patients with CHB. Clinicians should be aware of the limitations of RWE before applying it in research, but the method may be used across a wide spectrum of CHB research through judicious selection of data sources, refinement of study designs, and appropriate analytic approaches. This will bring researchers a step closer to optimizing the secondary prevention of HCC in patients with CHB.

DECLARATIONS

Authors' contributions

Responsible for the conception, review, drafting, and critical revision of the manuscript, and approved the final version of the manuscript: Lim J, Choi J

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Both authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication

Not applicable.

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