Antiviral Chemistry and Chemotherapy
2020, Vol. 28: 1–8

DOI: 10.1177/2040206620921331
journals.sagepub.com/home/avc
SAGE

Nucleos(t)ide analogues and Hepatitis B virus-related hepatocellular carcinoma: A literature review

Mohamed A Abd El Aziz[1], Rodolfo Sacco[2] and Antonio Facciorusso[2]

Abstract

Hepatitis B virus is mainly considered to cause hepatocellular carcinoma which is the fourth leading cause of cancer-related mortality worldwide. Treatment of Hepatitis B virus with nucleos(t)ide analogues can decrease the progression of the disease and subsequently decreases the incidence of hepatocellular carcinoma. In this review, we have discussed the different classes of nucleos(t)ide analogues used in the treatment of Hepatitis B virus and their relationship with the development of hepatocellular carcinoma. Furthermore, we discussed the effect of treatment of Hepatitis B virus with Nucleoside analogues (NAs) before, during and after surgery, chemoembolization, radiofrequency ablation, and chemotherapy for the treatment of hepatocellular carcinoma.

Keywords

Hepatocellular carcinoma, Hepatitis B virus, nucleos(t)ide analogues, lamivudine, adefovir, entecavir, tenofovir, telbivudine interferon

Date received: 12 January 2020; accepted: 1 April 2020

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide.[1] It is the fifth most common cancer diagnosed among adult men and the ninth most common cancer diagnosed among women.[1] Between 1990 and 2015 the incidence of liver cancer has increased by 75%.[2] Among all risk factors of HCC, Hepatitis B virus (HBV) is believed to be the leading cause of incident cases and mortality of HCC globally.[2,3]

HBV is a double-stranded DNA virus that can be transmitted perinatally from the mother to her child, through unprotected sexual intercourse, or through blood products (e.g. needle sticks).[4,5] After infection, the HBV transfers its DNA into the host's hepatocyte nucleus and starts using the organoids of the hepatocyte nucleus for its replication.[6] The random integration of the virus genome into the host's genome is considered the initiating incident for HCC development.[6] The nucleos(t)ide analogue drugs (NUCs) have been developed to block the HBV DVA polymerase enzyme, thus inhibiting the virus replication and further infection of the neighbor cells.[7] However, the protective mechanism of these drugs against the development of HCC is still questionable. The aim of the current study is to review the literature regarding whether treatment of HBV using NUCs helps prevent the development of HCC or not.

Lamivudine risk of HCC after treatment with nucleos(t)ide analogues

Lamivudine therapy. Data from a multicenter randomized controlled trial (RCT) have shown that treatment with lamivudine for a median duration of 32.4 months has decreased the incidence of HCC development

[1]Department of Surgery, Mayo Clinic, Rochester, MN, USA
[2]Department of Medical Sciences, Section of Gastroenterology, University of Foggia, Foggia Italy

Corresponding author:
Antonio Facciorusso, Department of Medical Sciences, Section of Gastroenterology, University of Foggia, Foggia, Italy.
Email: antonio.facciorusso@virgilio.it

compared to placebo 3.9% in lamivudine group versus 7.4% in the placebo group with an adjusted HR: 0.49 (0.25–0.99).[8] Even in patients with cirrhosis, lamivudine therapy has been shown to decrease the risk of HCC as shown in a retrospective analysis for 238 patients; the incidence of HCC in patients treated with lamivudine was 9.8% compared to 25% in the control group. In addition, the mortality was lower in patients treated with lamivudine compared to the control group.[9] The optimal duration of lamivudine therapy has become a matter of debate, and a study conducted by Kwon et al. has suggested that treatment for more than five years in patients who do not develop YMDD mutations may continue treatment for over five years until loss of HBV surface antigen (HBsAg).[10] However, the maintained viral response achieved by lamivudine treatment for more than five-years did not show a decrease in the incidence of HCC.[11] Nevertheless, about 43% of the included patients had liver cirrhosis at baseline which is known to be an independent risk factor for HCC development even in lamivudine-treated patients (OR = 12.1, 95% confidence interval (CI) 1.39 to 106.2).[12] On the other hand, Eun et al. have found that sustained viral suppression with long-term lamivudine therapy has decreased the incidence of HCC.[13] During treatment with lamivudine, resistance can develop which may be due to mutations in the viral DNA.[14] In this population, treatment with adefovir has been tried as an add-on therapy which showed a great success.[15] However, caution should be taken in patients with YIDD mutations and HBeAg-positive patients.[16,17] However, in patients with HBeAg negative, lamivudine has been shown to decrease the Child-Pugh scores in the first three years of follow-up. In addition, after lamivudine therapy, the incidence of HCC in cirrhotic patients with HBeAg negative was comparable to non-cirrhotic patients (13.2%).[18]

Impact on liver-related mortality. Lamivudine treatment has been shown to decrease the liver-related mortality in patients with HBV even in patients with co-infection with human immune deficiency virus (HIV).[19] Effective viral suppression has shown to reduce the risk of HCC development with a 10-year cumulative incidence of 15.73%.[20] However, baseline cirrhosis is known to be a significant risk factor for HCC with a 10-year incidence of 43.16% in cirrhotic patients versus 7.05% in non-cirrhotic patients.[20] Nevertheless, the achievement of viral suppression has decreased the incidence of HCC in cirrhotic patients (10-year incidence of 27.78% in cirrhotic patients who achieved viral suppression compared to 62.24% in cirrhotic patients who did not achieve viral suppression).[20] On the other hand, data from a larger sample size have shown that serological clearance has been only beneficial to patients without cirrhosis.[21]

Adefovir therapy. Adefovir is considered an option for patients with lamivudine resistance. Although adefovir alone therapy has been shown to be an effective treatment for HBV patients and its long-term use has been shown to decrease the fibrosis score, the emergence of resistance with its long-term use is a major limitation.[22] The combination between adefovir and lamivudine in patients with lamivudine resistance chronic HBV has shown a great success and lower mutations rate that might lead to adefovir resistance. In addition, the three-year follow-up has shown a 12% risk of developing HCC while 73% of the included patients had cirrhosis at baseline.[23]

Entecavir or tenofovir therapy. Entecavir treatment has been shown to decrease the incidence of HCC compared to non-treatment. The five-year incidence rate was 3.7% in entecavir group compared to 13.7% in the no-treatment group (adjusted HR: 0.37; 95% CI; (0.15–0.91)).[24] However, a retrospective analysis of 875 chronic HBV patients who were treated with entecavir monotherapy has shown that 43% of the treated patients did not achieve a maintained virological remission (MVR) (persistently undetectable HBV DNA ($<$12 IU/mL) and they were at a higher risk of developing HCC especially in patients with cirrhosis.[25] This finding might raise the concern to change the entecavir therapy if the patient did not achieve MVR during the treatment. For patients with cirrhosis, treatment with entecavir has resulted in a decrease in the incidence of HCC. However, the level of compensation affected the incidence of HCC (2.2% in compensated group versus 13.7% in the decompensated group).[26] Age $>$ 50 years old, male sex, high serum level of Procollagen III N-terminal peptide, and no virological response after 12 months of treatment were recognized as independent risk factors for developing HCC in patients with HBV-related cirrhosis treated with entecavir.[27] Nevertheless, a subgroup analysis according to the level of decompensation has revealed that no virological response after 12 months of treatment with entecavir is an independent risk factor for HCC development in decompensated patients but not in compensated cirrhosis patients.[27] Follow-up with serum alanine aminotransferase (ALT) at 6 months and 12 months is advised during treatment with entecavir . Normal ALT at 6 months and 12 months was found to have the least risk factor for the development of HCC.[28] In addition, surveillance using serum alpha-fetoprotein was advised. A cut off value of 13 ng/ml was found to have a positive predictive value of 77.8% and a

negative predictive value of 96.1% for the development of HCC in patients treated with entecavir.[29,30]

Entecavir as a second line rescue treatment after prior NUCs resistance has shown success. In addition, the virological clearance in these cases after treatment with entecavir was found to be a protective factor against the development of HCC.[31]

Data from an international RCT have shown that there were no differences between entecavir use and any other NUCs use on the incidence of HCC after follow-up for 10 years (0.87 (0.727–1.032)).[32] This finding was supported by data from retrospective studies.[33] However, in the Chinese population, tenofovir has been shown to be superior to entecavir in the prevention of HCC development (adjusted HR: 0.39; 95% CI; (0.18–0.84)).[34] Data from a recently published meta-analysis have shown that patients treated with tenofovir had a lower incidence of HCC compared to patients treated with entecavir (rate ratio: 0.66 (0.49–0.89)).[35] Tenofovir has been shown to be effective as a second line rescue therapy after lamivudine–adefovir failure.[36] Nevertheless, five (8%) patients with cirrhosis developed HCC after a median of 26.5 months of treatment with tenofovir after being treated with lamivudine–adefovir.[36]

Telbivudine therapy. The results of RCTs have shown that telbivudine was superior to lamivudine in the treatment of patients with chronic HBV regardless of HBeAg status.[37–39] In addition, results from several RCTs have shown the superiority of telbivudine over other NUCs such as entecavir[40,41] and adefovir.[42] However, in 2013, Tsai et al. found that the cumulative incidence of HCC development in patients treated with telbivudine was 2.5% and 4.1% at two and three years, respectively which was not statistically different from the results of patients treated with entecavir (3.1% and 7.5% at two and three years respectively; $P = 0.565$).[43] Nevertheless, the kidney function should be taken into consideration while choosing between the NUCs. Of note, telbivudine was found to be more effective in the prevention of nephrotoxicity.[44]

Interferon therapy. Data from an open-label RCT have shown that use of interferon-alpha with the NUCs for 96 weeks has resulted in increased clearance of HBsAg compared to NUCs alone. However, grade 3 and 4 adverse events were more frequently reported in the interferon group.[45] Moreover, data from retrospective studies have shown that interferon treatment is superior to NUCs in the suppression of viral load, HbsAg clearance and in the prevention of HCC.[46,47] Although they did not conduct a subgroup analysis according to the type of NUCs used, about 60% of patients in the NUCs group received entecavir only.[46] In a five-year observational study, the five-year cumulative incidence rate for HCC was lower in patients treated with interferon compared to entecavir.[48]

Putting all together. Data concerning the efficacy of different NUCs in reducing the risk of HCC are summirized in Table 1.

Prediction of HCC after treatment with nucleos(t)ide analogues

Several studies have been conducted to study the best method of HCC surveillance in HBV patients who are treated with NUCs.[49] For example, elevated serum Mac-2-binding protein glycosylation isomer after 48 weeks of antiviral therapy was found to be a predictive factor for the development of HCC which might warrant more close follow-up of these patients' population.[49] In these contexts, Hsu et al. developed a scoring system to predict the HCC occurrence in patients with HBV treated with NUCs. They found that there are four independent variables related to the risk which are cirrhosis, age, male gender and diabetes mellitus. They denoted to it with CAMD score[50] (Table 2). Patients with a score <8 have a three-year cumulative incidence for the development of HCC of 0.27% (95% CI 0.12–0.42%), compared to 2.40% (95% CI 2.03–2.78%), and 10.75% (95% CI 9.68–11.81%), in patients with a score of 8–13 and >13 respectively with AUC of 0.74 (95% CI) (0.71–0.76).[50,51] Similarly, several risk scores have been developed.[52–55]

Role of nucleos(t)ide analogues after treatment of HCC

Prophylaxis after liver transplantation. After liver transplantation for HBV-related HCC, recurrence of HBV was associated with a 3.6 fold increase in the HCC recurrence.[56] In these cases, prophylaxis with HBV immunoglobulin is recommended.[57] However, data from several meta-analyses have revealed the benefits of adding lamivudine to the HBV immunoglobulin with regard to HBV, HCC recurrence and survival rates.[58–60] Nevertheless, adding adefovir to the HBV immunoglobulin was found to be superior to lamivudine plus HBV immunoglobulin.[61] In addition, lower doses of HBV immunoglobulin could be given in the first week after the liver transplantation when adefovir is used compared to lamivudine.[61] Accordingly, adefovir was suggested as a therapeutic option after recurrence of HBV after liver transplantation or when resistance to lamivudine develops.[62,63]

After curative resection. Data from an RCT have shown that for patients with low HBV–DNA levels, antiviral

Table 1. Data concerning the efficacy of different NUCs in reducing the risk of HCC.

	Number of studies	Effect estimate (RR)	Heterogeneity level
Incidence of HCC in NUCs-treated chronic HBV patients			
ETV versus LAM	7	0.45 (0.3–0.67)	$I^2 = 43\%$
ETV versus LdT	3	0.72 (0.24–2.14)	$I^2 = 0\%$
ETV versus TDF	8	1.52 (0.95–2.44)	$I^2 = 40\%$
Biochemical response			
ETV versus LAM	1	1.32 (1.11–1.56)	NA
ETV versus LdT	1	1.09 (0.96–1.23)	NA
ETV versus TDF	2	1.06 (0.93–1.20)	$I^2 = 35\%$
Virological response			
ETV versus LAM	2	1.15 (1.03–1.29)	$I^2 = 30\%$
ETV versus LdT	2	1.37 (1.16–1.62)	$I^2 = 50\%$
ETV versus TDF	3	0.95 (0.86–1.05)	$I^2 = 44\%$
HBeAg serological conversion			
ETV versus LAM	1	1.01 (0.8–1.29)	NA
ETV versus LdT	2	1.36 (0.29–6.36)	$I^2 = 36\%$
ETV versus TDF	1	0.76 (0.42–1.4)	NA
Incidence of drug resistance			
ETV versus LAM	4	0.03 (0.02–0.04)	$I^2 = 0\%$
ETV versus LdT	2	0.04 (0.01–0.22)	$I^2 = 0\%$
ETV versus TDF	1	0.94 (0.14–6.46)	NA
Risk of HCC in patients with CHB treated with NUCs + LC versus CHB treated with NUCs without LC			
Wang et al., 2019	7	30.12 (1.79–506.24)	$I^2 = 22\%$

ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; LAM: lamivudine; ADV: adefovir dipivoxil; LdT: telbivudine; HCC: hepatocellular carcinoma; HBV: Hepatitis B virus; RR: risk ratio; HBeAg: Hepatitis B e-antigen; CHB: chronic Hepatitis B virus; LC: liver cirrhosis.
Biochemical response: normalization of the level of alanine aminotransferase as assessed by routine hepatic panel
Virological response: undetectable HBV DNA in an HBeAg-negative patient
Drug resistance: the reappearance of HBV DNA after a period of non-detectable HBV DNA.

Table 2. CAMD scoring system for the prediction of HCC in HBV patients treated with antiviral therapy.

Variable	CAMD score
Cirrhosis	
No cirrhosis	0
Cirrhosis with age <40 years	10
Cirrhosis with age ≥40 years	6
Age (years)	
<40	0
40–49	5
50–59	8
≥60	10
Sex	
Male	2
Female	0
Diabetes mellitus (DM)	
No DM	0
Presence of DM	1

CAMD: cirrhosis, age, male sex and diabetes mellitus.

therapy has been shown to reduce the recurrence of HCC after curative resection.[64] The 1-, 3-, and 5-year recurrence-free survival rates for patients treated with antiviral therapy were 85.9%, 55.2%, and 52% compared to 80.6%, 40.9%, and 32.3%, in the control group. In addition, the antiviral treatment was found to be an independent protective factor for recurrence (the adjusted hazard ratio (HR) = 0.316, 95% CI 0.157–0.637; P = 0.001).[64] Moreover, antiviral treatment after hepatectomy for patients who had HBV-related HCC has been shown to decrease the viral reactivation. The incidence of HBV reactivation was found to be 2.5% in the patients who have been treated with antiviral therapy compared to 31.8% in untreated patients.[65] This finding was supported by two meta-analyses.[66–68] However, subgroup analysis revealed that the improvement in the overall survival and the progression-free survival has only been found in patients with high baseline HBV DNA (≥20,000 IU/mL).[68] Of note, long-term adefovir therapy was associated with better overall survival and disease-free survival than long-term therapy with telbivudine in patients who had hepatectomy for HBV-related HCC.[69] Regarding the short-term post-operative complications after curative resection, perioperative antiviral therapy was found to reduce the patients' recovery time and the improvement of the liver function compared to non-treatment groups.[70] The improvement of

liver function and the progression-free survival after curative resection for HCC was found to be more likely in patients with HCC less than 3 cm in size.[71]

After chemoembolization. Lamivudine was found to decrease the HBV reactivation during chemoembolization. In an RCT, the HBV reactivation rate in the lamivudine group was 2.8% compared to 29.7% in the control group ($P = 0.002$).[72] On multivariate regression analysis, the baseline HBV DNA level of more than 10^4 copies/mL was the only predictor for reactivation.[72] Similarly, entecavir prophylactic therapy was found to decrease HBV reactivation with chemoembolization therapy.[73,74] However, females, HBeAg positive patients, number of tumors more than 3 and patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 were found to be at higher risk for developing reactivation without treatment.[73,75] Regarding survival after chemoembolization therapy, NUCs therapy was found to improve the 1-, 3-, and 5-year survival rates compared to non-treatment groups.[76–78]

After radiofrequency ablation. Treatment with NUCs has shown to reduce the two-year recurrence rate compared to the non-treated group (1.8%; 95% CI: 32.9–50.6 vs. 54.3%; 95% CI: 48.0–60.6; modified log-rank test: $P < 0.05$).[79] In multivariate cox proportional HR, the antiviral therapy was the only protective factor against recurrence (HR: 0.69; 95% CI [0.5–0.95]).[79]

With multikinase inhibitors. In patients treated with sorafenib, concurrent administration of antiviral therapy improved the overall survival compared to the non-treated group (16.47 months vs. 13.10 months, $P = 0.03$).[80] The benefit in the overall survival was noted to be more in patients with Barcelona Clinic Liver Cancer (BCLC) stage C and patients with higher HBV DNA level at baseline.[80]

Conclusion

Although we have tried to provide an extensive overview of this very broad topic, we did not pool the results of the studies that we discussed. Nevertheless, the use of NUCs in patients with HBV seems to be protective against the development of HCC. Further studies are needed to provide more information about an individualized selection of the NUCs based on the patients' characteristics.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Antonio Facciorusso https://orcid.org/0000-0002-2107-2156

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424. DOI: 10.3322/caac.21492.
2. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol* 2017; 3: 1683–1691.
3. Mittal S and El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol* 2013; 47: S2–6.
4. Ma L, Alla NR, Li X, et al. Mother-to-child transmission of HBV: review of current clinical management and prevention strategies. *Rev Med Virol* 2014; 24: 396–406.DOI: 10.1002/rmv.1801.
5. Piot P, Goilav C and Kegels E. Hepatitis B: transmission by sexual contact and needle sharing. *Vaccine* 1990; 8: S37–40. discussion S41–33. DOI: 10.1016/0264-410x(90)90215-8.
6. Tu T, Budzinska MA, Shackel NA, et al. HBV DNA integration: molecular mechanisms and clinical implications. *Viruses* 2017; 9: pii:E75.
7. Kim SS, Cheong JY and Cho SW. Current nucleos(t)ide analogue therapy for chronic Hepatitis B. *Gut Liver* 2011; 5: 278–287.
8. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic Hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351: 1521–1531. DOI: 10.1056/NEJMoa033364.
9. Su MH, Lu AL, Li SH, et al. Long-term lamivudine for chronic hepatitis B and cirrhosis: a real-life cohort study. *World J Gastroenterol* 2015; 21: 13087–13094.DOI: 10.3748/wjg.v21.i46.13087.
10. Kwon JH, Jang JW, Choi JY, et al. Should lamivudine monotherapy be stopped or continued in patients infected with hepatitis B with favorable responses after more than 5 years of treatment? *J Med Virol* 2013; 85: 34–42. DOI: 10.1002/jmv.23421.
11. Kurokawa M, Hiramatsu N, Oze T, et al. Long-term effect of lamivudine treatment on the incidence of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Gastroenterol* 2012; 47: 577–585. DOI: 10.1007/s00535-011-0522-7.
12. Pellicelli AM, Vignally P, Messina V, et al. Long term nucleotide and nucleoside analogs treatment in chronic hepatitis B HBeAg negative genotype D patients and risk

for hepatocellular carcinoma. *Ann Hepatol* 2014; 13: 376–385. DOI: 10.1016/s1665-2681(19)30844-0.
13. Eun JR, Lee HJ, Kim TN, et al. Risk assessment for the development of hepatocellular carcinoma: according to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease. *J Hepatol* 2010; 53: 118–125. DOI: 10.1016/j.jhep.2010.02.026.
14. Kumashiro R, Kuwahara R, Ide T, et al. Subclones of drug-resistant hepatitis B virus mutants and the outcome of breakthrough hepatitis in patients treated with lamivudine. *Intervirology* 2003; 46: 350–354. DOI: 10.1159/000074991.
15. Akuta N, Suzuki F, Kawamura Y, et al. Virological response and hepatocarcinogenesis in lamivudine-resistant hepatitis B virus genotype C patients treated with lamivudine plus adefovir dipivoxil. *Intervirology* 2008; 51: 385–393. DOI: 10.1159/000203283.
16. Andreone P, Gramenzi A, Cursaro C, et al. High risk of hepatocellular carcinoma in anti-HBe positive liver cirrhosis patients developing lamivudine resistance. *J Viral Hepat* 2004; 11: 439–442. DOI: 10.1111/j.1365-2893.2004.00564.x.
17. Hosaka T, Suzuki F, Kobayashi M, et al. Development of HCC in patients receiving adefovir dipivoxil for lamivudine-resistant hepatitis B virus mutants. *Hepatol Res* 2010; 40: 145–152. DOI: 10.1111/j.1872-034X.2009.00582.x.
18. Kilic ZM, Kuran S, Akdogan M, et al. The long-term effects of lamivudine treatment in patients with HBeAg-negative liver cirrhosis. *Adv Therapy* 2008; 25: 190–200. DOI: 10.1007/s12325-008-0038-6.
19. Puoti M, Cozzi-Lepri A, Paraninfo G, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis. *Antivir Ther (Lond)* 2006; 11: 567–574.
20. Zhang W, Wang X, Wang Y, et al. Effective viral suppression is necessary to reduce hepatocellular carcinoma development in cirrhotic patients with chronic hepatitis B. *Medicine* 2017; 96: e8454. DOI: 10.1097/md.0000000000008454.
21. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011; 60: 1109–1116. DOI: 10.1136/gut.2010.221846.
22. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006; 131: 1743–1751. DOI: 10.1053/j.gastro.2006.09.020.
23. Lampertico P, Vigano M, Manenti E, et al. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology* 2007; 133: 1445–1451. DOI: 10.1053/j.gastro.2007.08.079.
24. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; 58: 98–107. DOI: 10.1002/hep.26180.
25. Kim JH, Sinn DH, Kang W, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. *Hepatology* 2017; 66: 335–343. DOI: 10.1002/hep.28916.
26. Gai XD and Wu WF. Effect of entecavir in the treatment of patients with hepatitis B virus-related compensated and decompensated cirrhosis. *Exp Ther Med* 2017; 14: 3908–3914. DOI: 10.3892/etm.2017.4963.
27. Kim SS, Hwang JC, Lim SG, et al. Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. *Am J Gastroenterol* 2014; 109: 1223–1233. DOI: 10.1038/ajg.2014.145.
28. Kim EJ, Yeon JE, Kwon OS, et al. Rapid alanine aminotransferase normalization with entecavir and hepatocellular carcinoma in hepatitis B virus-associated cirrhosis. *Dig Dis Sci* 2016; 62: 808–816. DOI: 10.1007/s10620-016-4431-8.
29. Kim GA, Seock CH, Park JW, et al. Reappraisal of serum alpha-foetoprotein as a surveillance test for hepatocellular carcinoma during entecavir treatment. *Liver Int* 2015; 35: 232–239. DOI: 10.1111/liv.12516.
30. Yamada R, Hiramatsu N, Oze T, et al. Impact of alpha-fetoprotein on hepatocellular carcinoma development during entecavir treatment of chronic hepatitis B virus infection. *J Gastroenterol* 2015; 5, 785–794. DOI: 10.1007/s00535-014-1010-7.
31. Yang SC, Lee CM, Hu TH, et al. Virological response to entecavir reduces the risk of liver disease progression in nucleos(t)ide analogue-experienced HBV-infected patients with prior resistant mutants. *J Antimicrob Chemother* 2013; 68: 2154–2163. DOI: 10.1093/jac/dkt147.
32. Hou JL, Zhao W, Lee C, et al. Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a randomized trial in 24 countries. *Clin Gastroenterol Hepatol* 2019; 18: 457–467. DOI: 10.1016/j.cgh.2019.07.010.
33. Koklu S, Tuna Y, Gulsen MT, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. *Clin Gastroenterol Hepatol* 2013; 11: 88–94. DOI: 10.1016/j.cgh.2012.10.003.
34. Yip TC, Wong VW, Chan HL, et al. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. *Gastroenterology* 2020; 158: 215–225 e216. DOI: 10.1053/j.gastro.2019.09.025.
35. Zhang Z, Zhou Y, Yang J, et al. The effectiveness of TDF versus ETV on incidence of HCC in CHB patients: a meta analysis. *BMC Cancer* 2019; 19: 511. DOI: 10.1186/s12885-019-5735-9.

36. Fasano M, Maggi P, Leone A, et al. Long-term efficacy and safety of switching from lamivudine + adefovir to tenofovir disoproxil fumarate in virologically suppressed patients. *Dig Liver Dis* 2017; 49: 530–534. DOI: 10.1016/j.dld.2017.01.140.
37. Liaw YF, Gane E, Leung N, et al. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; 136: 486–495. DOI: 10.1053/j.gastro.2008.10.026.
38. Lai CL, Gane E, Liaw YF, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; 357: 2576–2588. DOI: 10.1056/NEJMoa066422.
39. Hou J, Yin YK, Xu D, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: results at 1 year of a randomized, double-blind trial. *Hepatology* 2008; 47: 447–454. DOI: 10.1002/hep.22075.
40. Luo XD, Chen XF, Zhou Y, et al. Comparison of 208-week sequential therapy with telbivudine and entecavir in HBeAg-positive chronic hepatitis B patients with suboptimal responses to 24 weeks of Peg-IFNalpha-2a therapy: an open-labelled, randomized, controlled, "real-life" trial. *J Viral Hepat* 2017; 24: 36–42. DOI: 10.1111/jvh.12790.
41. Luo XD, Chen XP, Chen R, et al. Efficacy of 104-week sequential therapy with telbivudine or entecavir in HBeAg-positive chronic hepatitis B patients with suboptimal responses to 24-week therapy with pegylated interferon-alpha-2a. *Zhonghua Gan Zang Bing za Zhi = Zhonghua Ganzangbing Zazhi = Chin J Hepatol* 2016; 24: 241–245. DOI: 10.3760/cma.j.issn.1007-3418.2016.04.001.
42. Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. *Ann Intern Med* 2007; 147: 745–754. DOI: 10.7326/0003-4819-147-11-200712040-00183.
43. Tsai MC, Chen CH, Hung CH, et al. A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match-control study. *Clin Microbiol Infect: Off Publ Eur Soc Clin Microbiol Infect Dis* 2014; 20: O90–O100. DOI: 10.1111/1469-0691.12220.
44. Gane EJ, Deray G, Liaw YF, et al. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014; 146: 138–146.e135. DOI: 10.1053/j.gastro.2013.09.031.
45. Bourlière M, Rabiega P, Ganne-Carrie N, et al. Effect on HBs antigen clearance of addition of pegylated interferon alfa-2a to nucleos(t)ide analogue therapy versus nucleos (t)ide analogue therapy alone in patients with HBe antigen-negative chronic hepatitis B and sustained undetectable plasma hepatitis B virus DNA: a randomised, controlled, open-label trial. *Lancet Gastroenterol Hepatol* 2017; 2: 177–188. DOI: 10.1016/s2468-1253(16)30189-3.
46. Liang K-H, Hsu C-W, Chang M-L, et al. Peginterferon is superior to nucleos(t)ide analogues for prevention of hepatocellular carcinoma in chronic hepatitis B. *J Infect Dis* 2016; 213: 966–974. DOI: 10.1093/infdis/jiv547.
47. Ren P, Cao Z, Mo R, et al. Interferon-based treatment is superior to nucleos(t)ide analog in reducing HBV-related hepatocellular carcinoma for chronic hepatitis B patients at high risk. *Expert Opin Biol Ther* 2018; 18: 1085–1094. DOI: 10.1080/14712598.2018.1518423.
48. Li SY, Li H, Xiong YL, et al. Peginterferon is preferable to entecavir for prevention of unfavourable events in patients with HBeAg-positive chronic hepatitis B: a five-year observational cohort study. *J Viral Hepat* 2017; 24: 12–20. DOI: 10.1111/jvh.12755.
49. Shinkai N, Nojima M, Iio E, et al. High levels of serum Mac-2-binding protein glycosylation isomer (M2BPGi) predict the development of hepatocellular carcinoma in hepatitis B patients treated with nucleot(s)ide analogues. *J Gastroenterol* 2018; 53: 883–889. DOI: 10.1007/s00535-017-1424-0.
50. Hsu YC, Yip TC, Ho HJ, et al. Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. *J Hepatol* 2018; 69: 278–285. DOI: 10.1016/j.jhep.2018.02.032.
51. Kim SU, Seo YS, Lee HA, et al. Validation of the CAMD score in patients with chronic hepatitis b virus infection receiving antiviral therapy. *Clin Gastroenterol Hepatol* 2020; 18: 693–699. DOI: 10.1016/j.cgh.2019.06.028.
52. Wong GL, Chan HL, Chan HY, et al. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. *Gastroenterology* 2013; 144: 933–944. DOI: 10.1053/j.gastro.2013.02.002.
53. Riveiro-Barciela M, Tabernero D, Calleja JL, et al. Effectiveness and safety of entecavir or tenofovir in a Spanish cohort of chronic hepatitis B patients: validation of the Page-B Score to predict hepatocellular carcinoma. *Dig Dis Sci* 2017; 62: 784–793. DOI: 10.1007/s10620-017-4448-7.
54. Nishikawa H, Nishijima N, Enomoto H, et al. A predictive model for carcinogenesis in patients with chronic hepatitis B undergoing entecavir therapy and its validation. *Medicine (Baltimore)* 2016; 95: e4832–08. DOI: 10.1097/MD.0000000000004832.
55. Sohn W, Cho JY, Kim JH, et al. Risk score model for the development of hepatocellular carcinoma in treatment-naive patients receiving oral antiviral treatment for chronic hepatitis B. *Clin Mol Hepatol* 2017; 23: 170–178. DOI: 10.3350/cmh.2016.0086.
56. Campsen J, Zimmerman M, Trotter J, et al. Liver transplantation for hepatitis B liver disease and concomitant hepatocellular carcinoma in the United States With hepatitis B immunoglobulin and nucleoside/nucleotide analogues. *Liver Transpl* 2013; 19: 1020–1029. DOI: 10.1002/lt.23703.
57. Beckebaum S, Herzer K, Bauhofer A, et al. Recurrence of hepatitis B infection in liver transplant patients receiving long-term hepatitis B immunoglobulin prophylaxis. *Ann Transplant* 2018; 23: 789–801. DOI: 10.12659/AOT.910176.
58. Wang P, Tam N, Wang H, et al. Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B

recurrence after liver transplantation? A meta-analysis. *PloS One* 2014; 9: e1044802014/08/08. DOI: 10.1371/journal.pone.0104480.
59. Katz LH, Paul M, Guy DG, et al. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. *Transpl Infect Dis* 2010; 12: 292–308. DOI: 10.1111/j.1399-3062.2009.00470.x.
60. Loomba R, Rowley AK, Wesley R, et al. Hepatitis B immunoglobulin and lamivudine improve hepatitis B-related outcomes after liver transplantation: meta-analysis. *Clin Gastroenterol Hepatol* 2008; 6: 696–700. DOI: 10.1016/j.cgh.2008.02.055.
61. Cholongitas E, Goulis J, Akriviadis E, et al. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis B virus recurrence after liver transplantation: a systematic review. *Liver Transpl* 2011; 17: 1176–1190. DOI: 10.1002/lt.22354.
62. Akyildiz M, Karasu Z, Zeytunlu M, et al. Adefovir dipivoxil therapy in liver transplant recipients for recurrence of hepatitis B virus infection despite lamivudine plus hepatitis B immunoglobulin prophylaxis. *J Gastroenterol Hepatol* 2007; 22: 2130–2134. DOI: 10.1111/j.1440-1746.2006.04609.x.
63. Shen S. Prophylaxis against hepatitis B virus recurrence after liver transplantation: a registry study. *Wjg* 2015; 21: 584 DOI: 10.3748/wjg.v21.i2.
64. Huang G, Li PP, Lau WY, et al. Antiviral therapy reduces hepatocellular carcinoma recurrence in patients with low HBV-DNA levels: a randomized controlled trial. *Ann Surg* 2018; 268: 943–954. DOI: 10.1097/SLA.0000000000002727.
65. Huang L, Li J, Yan J, et al. Antiviral therapy decreases viral reactivation in patients with hepatitis B virus-related hepatocellular carcinoma undergoing hepatectomy: a randomized controlled trial. *J Viral Hepat* 2013; 20: 336–342. DOI: 10.1111/jvh.12036.
66. Zhang H, Zhou Y, Yuan G, et al. Antiviral therapy improves the survival rate and decreases recurrences and fatalities in liver cancer patients following curative resection: a meta-analysis. *Mol Clin Oncol* 2015; 3: 1239–1247. DOI: 10.3892/mco.2015.614.
67. Zhang G, Yu X, Liu P, et al. Efficacy of nucleoside analogs for chronic hepatitis B virus-related hepatocellular carcinoma after curative treatment: a meta-analysis. *Dig Dis Sci* 2018; 63: 3207–3219. DOI: 10.1007/s10620-018-5252-8.
68. Chen XX, Cheng JW, Huang A, et al. The effect of antiviral therapy on patients with hepatitis B virus-related hepatocellular carcinoma after curative resection: a systematic review and meta-analysis. *Onco Targets Ther* 2017; 10: 5363–5375. DOI: 10.2147/OTT.S150281.
69. He L, Xia Z, Shen J, et al. The different effects of adefovir dipivoxil and telbivudine on the prognosis of hepatitis B virus-related hepatocellular carcinoma patients after curative resection. *Medicine (Baltimore)* 2019; 98: e14386–09. DOI: 10.1097/MD.0000000000014386.
70. Zhang B, Xu D, Wang R, et al. Perioperative antiviral therapy improves safety in patients with hepatitis B related HCC following hepatectomy. *Int J Surg* 2015; 15: 1–5. DOI: 10.1016/j.ijsu.2014.12.030.
71. Zhang ZY, Zhou ZQ and Zhou GW. Higher efficacy of antiviral therapy after major hepatectomy in patients with hepatitis B virus-related hepatocellular carcinoma of less than 3 cm. *Eur J Gastroenterol Hepatol* 2014; 26: 1116–1124. DOI: 10.1097/MEG.0000000000000153.
72. Jang JW, Choi JY, Bae SH, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology* 2006; 43: 233–240. DOI: 10.1002/hep.21024.
73. Li X, Zhong X, Chen ZH, et al. Efficacy of prophylactic entecavir for hepatitis B virus-related hepatocellular carcinoma receiving transcatheter arterial chemoembolization. *Asian Pac J Cancer Prev* 2015; 16: 8665–8670. DOI: 10.7314/apjcp.2015.16.18.8665.
74. Yoo SH, Jang JW, Kwon JH, et al. Preemptive antiviral therapy with entecavir can reduce acute deterioration of hepatic function following transarterial chemoembolization. *Clin Mol Hepatol* 2016; 22: 458–465. DOI: 10.3350/cmh.2016.0054.
75. Wang K, Jiang G, Jia Z, et al. Effects of transarterial chemoembolization combined with antiviral therapy on HBV reactivation and liver function in HBV-related hepatocellular carcinoma patients with HBV-DNA negative. *Medicine (Baltimore)* 2018; 97: e109402018/06/01. DOI: 10.1097/MD.0000000000010940.
76. Toyoda H, Kumada T, Tada T, et al. Transarterial chemoembolization for hepatitis B virus-associated hepatocellular carcinoma: improved survival after concomitant treatment with nucleoside analogues. *J Vasc Interv Radiol* 2012; 23: 317–322. e311. DOI: 10.1016/j.jvir.2011.11.012.
77. Xu X, Huang P, Tian H, et al. Role of lamivudine with transarterial chemoembolization in the survival of patients with hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014; 29: 1273–1278. DOI: 10.1111/jgh.12554.
78. Zhu SL, Zhong JH, Ke Y, et al. Comparative efficacy of postoperative transarterial chemoembolization with or without antiviral therapy for hepatitis B virus-related hepatocellular carcinoma. *Tumour Biol* 2015; 36: 6277–6284. DOI: 10.1007/s13277-015-3313-6.
79. Lee TY, Lin JT, Zeng YS, et al. Association between nucleos(t)ide analog and tumor recurrence in hepatitis B virus-related hepatocellular carcinoma after radiofrequency ablation. *Hepatology* 2016; 63: 1517–1527. DOI: 10.1002/hep.28266.
80. Xu L, Gao H, Huang J, et al. Antiviral therapy in the improvement of survival of patients with hepatitis B virus-related hepatocellular carcinoma treated with sorafenib. *J Gastroenterol Hepatol* 2015; 30: 1032–1039. DOI: 10.1111/jgh.12910.