ORIGINAL ARTICLE

Entecavir and Low Genetic Barrier Antiviral Agents for Hepatocellular Carcinoma in Hepatitis B Viral Cirrhosis: Propensity Score Matching

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ABSTRACT

Objective: To compare the reduction of hepatocellular carcinoma (HCC) risk between long-term treatment of entecavir and low genetic barrier antiviral agents in hepatitis B virus (HBV)-related cirrhotic patients.
Study Design: An observational study.
Place and Duration of Study: Department of Infectious Diseases and Hepatology, the Second Hospital of Shandong University, Jinan, China, from October 2008 to October 2016.
Methodology: HBV-related cirrhotic patients with antiviral treatment for at least 12 months were consecutively included. Propensity score matching analysis was performed to improve comparability of the data from both entecavir group and the control group. Log-rank test was used to compare influence of various nucleos(t)ide analogs (NAs) for incidence of HCC. Independent risk factors were estimated by multivariable Cox proportional hazards models.
Results: The total cohort included 207 HBV-related cirrhotic patients, of which 83 patients were treated with entecavir initially. The present study found no statistical difference for the incidence of HCC between entecavir group and the control group in the total cohort (p=0.525). However, the difference became statistically significant (p=0.014) after propensity score matching. Number needed to treat (NNT) were 8 patients, 6 patients and 3 patients at years 2, 3 and 4, respectively. Multivariable Cox regression in propensity score matching cohort revealed older age (HR: 1.066, p=0.041), NAs of low generic barrier (HR: 6.944, p=0.016), NAs resistance (HR: 3.648, p=0.041), and lower platelet counts (<80x10^9/L) (HR: 6.718, p=0.009) as independent risk factors for HCC incidence.
Conclusion: Entecavir is more efficient in reducing the incident HCC risk for HBV-related cirrhotic patients in comparison to low genetic barrier NAs.

Key Words: Hepatocellular carcinoma, Liver cirrhosis, Hepatitis B virus, Entecavir, Comparative effectiveness research.

INTRODUCTION

About 240 million people worldwide have been chronically infected with hepatitis B virus (HBV). The infection rate is disturbingly high in the Asian Pacific region.[1] Chronic hepatitis B (CHB) infection increases the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Previous researches reveal that around 15-40% of the infected people suffer from severe diseases caused by hepatitis B.[1] To prevent tragic consequences of hepatitis B infection such as cirrhosis, hepatic decompensation, end-stage liver disease, HCC and death, antiviral therapy is widely used.[1]

Within the past 10-20 years, five oral nucleos(t)ide analogs (NAs) have been proved as efficient antiviral drugs. According to previous studies, lamivudine is able to significantly reduce mortality and to prevent the

occurrence of HCC in patients with CHB compared with no antiviral treatment.[2] Entecavir, a relatively new antiviral agent with high genetic barrier, has been proved to suppress HBV DNA replications effectively with relatively low drug-resistance rate.[3] It is also reported that the incidence of HCC in CHB patients has been significantly reduced by entecavir.[4] Although low genetic barrier agents (lamivudine, adefovir and telbivudine) have not been recommended as preferred regimens by current guidelines, they are still widely used considering the cost and availability of NAs, especially in some parts of Asia and Africa.[5] Even different genetic barriers, and several studies did not show any obvious difference for the incidence of HCC in patients with CHB or cirrhosis when they were treated with lamivudine or entecavir.[6-8] It has also been noticed that some studies showed the HCC suppression effect of entecavir was greater than that of lamivudine.[4] The inconsistent conclusions make clinicians puzzled whether higher genetic barriers are equal to more significant HCC suppression effect. Meanwhile, the question which merits further discussion is that whether current evidence is conclusive enough to persuade cirrhotic patients with acceptable antiviral effect caused by low generic barrier NAs to be treated with high genetic barrier NAs. Further studies deriving from clinical practice are greatly needed. The usage of

propensity score matching makes it possible to reduce bias due to confounding factors in real-world observational studies. Furthermore, uptill now, most of similar studies have focused on the comparison for incidence of HCC with entecavir and lamivudine, without other low genetic barrier drugs such as adefovir and telbivudine, which is not in conformity with the clinical practice.

The purpose of the present study was to compare the reduction of HCC risk between long-term treatment of entecavir and low genetic barrier drugs (lamivudine, adefovir and telbivudine) in HBV-related cirrhotic patients by a propensity score matching analysis.

METHODOLOGY

This study was a retrospective collection of observational data. Consecutive HBV-related cirrhotic patients with antiviral therapy for at least 12 months were retrospectively evaluated and enrolled to Department of Infectious Diseases and Hepatology, the Second Hospital of Shandong University, Jinan, China between October 2008 and October 2016. All included patients were treatment *naïve* and were initially treated with NAs (lamivudine, adefovir, telbivudine or entecavir). Patients initially treated with lamivudine plus adefovir or lamivudine plus interferon were also included. It was also required that the patients being selected show hepatitis B surface antigen (HBsAg) positive for at least 6 months before the commencement of the antiviral therapy. To ensure the accuracy of the results, those who were co-infected with other virus (e.g. hepatitis C virus, human immunodeficiency virus) or combined with other liver diseases (e.g. autoimmune hepatitis, drug-induced-liver disease), and patients with HCC during the first year of NAs therapy were excluded. The 1-year interval was established to minimize the risk of both inclusion of preexisting HCC for analyses and inappropriate attribution of antiviral effect.[8,9] This study protocol followed guidelines of the Helsinki Declaration and has been approved by the Institutional Review Board of the Second Hospital of Shandong University. Patients were regularly monitored every 3 to 6 months and the following inspection items were performed: liver biochemistry examination, international normalized ratio (INR), α-fetoprotein (AFP) level, serum HBV DNA, hepatitis B e antigen (HBeAg) and imaging examinations (ultrasound, CT, or MRI). The observational outcome of this study was the occurrence of HCC in entecavir group and control group (patients treated with low genetic barrier drugs: lamivudine, adefovir and telbivudine. Lamivudine plus adefovir or lamivudine plus interferon were also included). HCC was defined as a tumor with a maximum diameter more than 2 cm and typical features of HCC with arterial hypervascularity and venous or delayed phase washout using CT or MRI, or nodules of 1-2 cm and typical features of HCC with two coincident imaging techniques (CT and MRI).

Serum alanine aminotransferase (ALT), aspartate amino-transferase (AST), bilirubin were measured by Beckman CX7 Chemistry Analyzer (Beckman Coulter, CA, USA) and original reagents. HBsAg, antibody against HBsAg (anti-HBs), hepatitis B e antigen (HBeAg) and antibody against HBeAg (anti-HBe) were detected with a commercial radioimmunoassay kit (Abbott Laboratories, Abbott Park, IL, USA). Serum HBV DNA levels were detected by using real-time PCR with suitable reagents (Sinomd Gene, Beijing, China). The lowest detection limit of HBV DNA was 500 copies/ml.

The propensity score matching analysis was applied to improve the comparability of the data from both entecavir group and control group. A propensity score of each patient was calculated by using logistic regression, covariates included in the multivariable logistic regression analysis, model were age, gender, status of HBeAg, HBV DNA, ALT, AST, bilirubin, AFP, platelet count, INR, history of alcohol intake, family history of HCC, NAs resistance and follow-up duration. We used 1:1 nearest-neighbor matching and the match tolerance between two participants was 0.05. Patients failed to match were excluded. Log-rank test was performed to compare the influence of different NAs on the incidence of HCC.

The normality of continuous variables was evaluated by Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median interquartile range (IQR) and were compared with t-test or Mann-Whitney U-test as appropriate. Categorical data was compared with χ^2 test or Fisher's exact test. Logarithmic transformation was performed at HBV DNA level for further statistical analysis. Survival curves were generated by Kaplan-Meier method. Independent risk factors were evaluated by multivariable Cox proportional hazard models (Forward LR method). Number needed to treat NNT to prevent 1 additional occurrence of HCC comparing entecavir with low genetic barrier drugs was also calculated according to the method of Altman *et al*.[10] A p-value <0.05 (two-tailed) implied statistically significance. All statistical analyses were performed by using IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The total cohort included 207 HBV-related cirrhotic patients, of which 83 patients were treated with entecavir initially (entecavir group). For the other 124 cirrhotic patients (control group: patients treated with NAs of lower genetic barrier), the initial NAs were lamivudine in 42 patients, adefovir in 74 patients, telbivudine in five patients, lamivudine plus adefovir in two patients and lamivudine plus interferon in one patient. Patients in the entecavir group were typical of lower incidence of NAs resistance (p<0.001) and shorter follow-up duration (p<0.001) in comparison to those in the control group (Table I).

HCC occurred in 30 (14.5%) of the 207 cirrhotic patients during a median of 31 (IQR 19-49) months' follow-up. Among those patients, 7 patients (8.4%) were from entecavir group and 23 patients (18.5%) were from the control group (Table II). For patients in entecavir group and patients in control group (treated with low genetic barrier drugs), the cumulative incidence rate of HCC at months 24, 36, and 48 by Kaplan-Meier analysis were 8.7%, 12.6%, 12.6% and 5.5%, 10.0%, 16.2%, respectively. Log-rank test revealed no statistical difference for the incidence rate of HCC between the above two groups (p=0.525, Figure 1).

As for baseline characteristics, an imbalance existed between entecavir group and the control group. To correct the above imbalance, a propensity score matching analysis was applied according to several baseline characteristics. The propensity score matching cohort yielded 112 (56 pairs) of cirrhotic patients. The median follow-up duration in entecavir group and that in the control group were 28.0 (IQR 18.0-36.0) months and 25.0 (IQR 18.0-35.0) months, respectively (p=0.731). The incidence of NAs resistance were 7.1% (4 patients) and 19.6% (11 patients) in the two groups (p=0.052). We believed that the baseline characteristics were comparable between entecavir group and the control group after the performance of propensity score matching (Table I).

In the propensity score matching cohort, 13 (11.6%) cirrhotic patients developed HCC. Among them, 2 patients (3.6%) belonged to entecavir group and 11 patients (19.6%) belonged to the control group (Table II). For patients in entecavir group and patients in control group, the cumulative incidence rate of HCC at months 24, 36, and 48 were 2.3%, 6.7%, 6.7% and 14.5%,

Table I: Characteristics of the total cohort and propensity score-matched cohort.

	Total cohort			Propensity score-matched cohort		
	Entecavir (n=83)	Drugs with lower generic barrier (n=124)	p-value	Entecavir (n=56)	Drugs with lower generic barrier (n=56)	p-value
Age (years)	48.8 ±11.1	48.3 ±12.1	0.779	48.2 ±11.2	48.2 ±13.0	0.988
Gender						
Male (n,%)	59 (71.1%)	84 (67.7%)	0.610	39 (69.6%)	41 (73.2%)	0.676
Female (n,%)	24 (28.9%)	40 (32.3%)		17 (30.4%)	15 (26.8%)	
HBeAg						
Positive	53 (63.9%)	70 (56.5%)	0.288	33 (58.9%)	34 (60.7%)	0.847
Negative	30 (36.1%)	54 (43.5%)		2 (41.1%)	22 (39.3%)	
HBV DNA (log$_{10}$copy/ml)	5.8 ±1.5	5.7±1.2	0.375	5.6 ±1.5	5.9 ±1.3	0.216
ALT(U/L), median (IQR)	59.0 (34.0-119.0)	60.0 (39.0-113.0)	0.760	57.0 (31.0-97.0)	73.0 (45.0-141.0)	.033
AST(U/L), median (IQR)	60.0 (45.0-110.0)	62.0 (46.0-125.0)	0.564	57.0 (42.0-106.0)	62.0 (48.0-135.0)	0.164
Bilirubin (umol/L), median (IQR)	30.2 (19.2-48.4)	33.1 (18.3-58.1)	0.730	28.3 (19.0-40.8)	33.8 (20.2-56.6)	0.253
Platelet count (10^9/L), median (IQR)	91.0 (57.0-119.0)	74.0(52.3-112.3)	0.215	75.0 (55.0-103.0)	82.0 (47.0-112.0)	0.928
INR, median (IQR)	1.16 (1.05-1.36)	1.20 (1.03-1.47)	0.579	1.18 (1.04-1.34)	1.20 (1.04-1.40)	0.880
AFP (ng/ml), median (IQR)	9.4 (4.9-50.4)	11.4 (4.2-43.8)	0.878	8.0 (4.2-40.4)	12.1 (5.1-48.1)	0.231
History of:						
Alcohol intake (n, %)	22 (26.5%)	32 (25.8%)	0.911	15 (26.8%)	16 (28.6%)	0.833
No alcohol intake (n, %)	61 (73.5%)	92 (74.2%)			41 (73.2%)	40 (71.4%)
Family history of						
HCC (n, %)	8 (9.6%)	7 (5.6%)	0.277	5 (8.9%)	4 (7.1%)	.000
No HCC (n, %)	75 (90.4%)	117 (94.4%)		51 (91.1%)	52 (92.9%)	
NAs resistance						
Yes (n, %)	5 (6.0%)	32 (25.8%)	<0.001	4 (7.1%)	11 (19.6%)	0.052
No (n, %)	78 (94.0%)	92 (74.2%)	<0.001	52 (92.9%)	45 (80.4%)	
Follow-up duration, months, median (IQR)	22.0 (17.0-34.0)	40.0 (26.0-60.0)	<0.001	28.0 (18.0-36.0)	25.0 (18.0-35.0)	0.731

HBeAg = Hepatitis B e antigen; HBV = Hepatitis B virus; ALT = Alanine aminotransferase; AST = Aspartateaminotransferas; AFP = Alphafetoprotein; INR = International normalized ratio; HCC = Hepatocellular carcinoma; IQR = Interquartile range.

Table II: Treatment strategies in control group (patients treated with NAs of lower genetic barrier).

Treatment strategies	Total cohort (n,%)		Propensity score-matched cohort (n,%)	
	No. of patients (n=124)	No. of patients with HCC (n=23)	No. of patients (n=56)	No. of patients with HCC (n=11)
Lamivudine	42 (33.9%)	9 (39.1%)	21 (37.5%)	5 (45.5%)
Adefovir	74 (59.7%)	13 (56.5%)	28 (50.0%)	5 (45.5%)
Telbivudine	5 (4.0%)	1 (4.3%)	4 (7.1%)	1 (9.1%)
Lamivudine plus adefovir	2 (1.6%)	0 (0.0%)	2 (3.6%)	0 (0.0%)
Lamivudine plus interferon	1 (0.8%)	0 (0.0%)	1 (1.8%)	0 (0.0%)

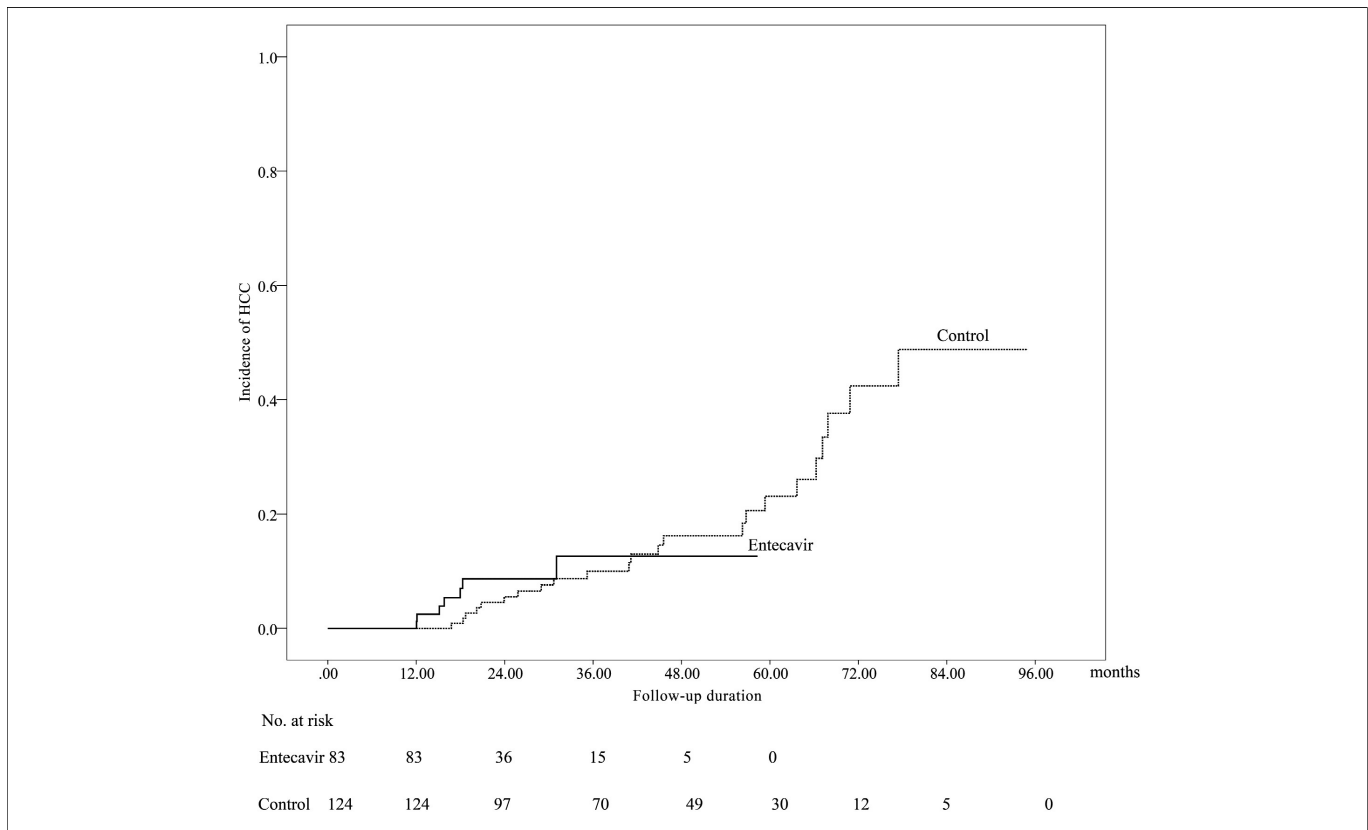*NAs = Nucleos(t)ide analogs; HCC = Hepatocellular carcinoma.*

Figure 1: Cumulative incidence of HCC for entecavir group and control group in the total cohort (207 patients).
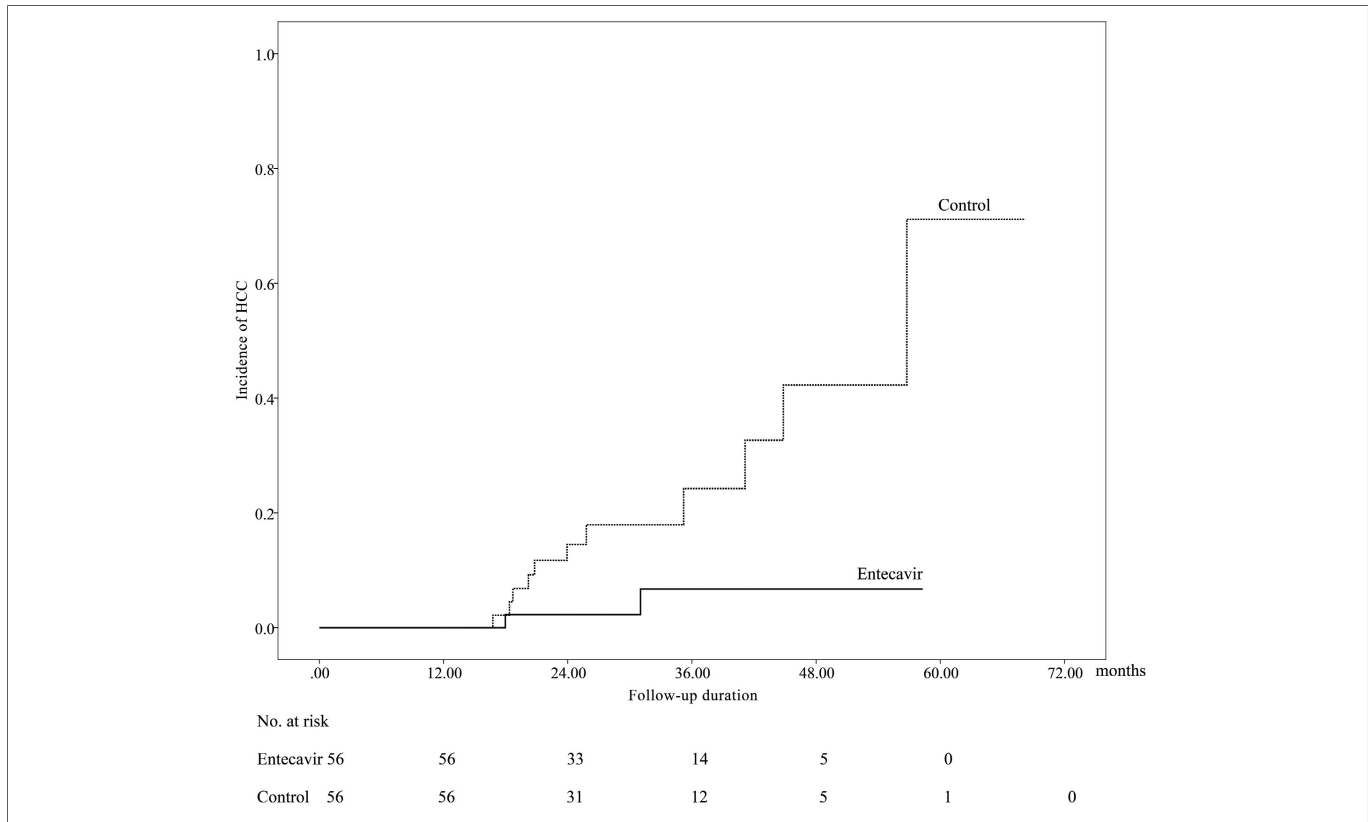

Figure 2: Cumulative incidence of HCC for entecavir group and control group in the propensity score matching cohort (112 patients).

24.2%, 42.3%, respectively, yielding NNT of 8 patients, 6 patients and 3 patients at years 2, 3 and 4, respectively. The difference between the two groups for the incidence rate of HCC was statistically significant according to the results of Log-rank test (p=0.014, Figure 2). The risk of HCC was also evaluated by multivariable Cox regression in this propensity score matching cohort adjusted for different NAs. Older age (HR: 1.066, 95%CI 1.002-1.134, p=0.041), NAs of low generic barrier (HR: 6.944, 95%CI 1.427-34.483, p=0.016), NAs resistance (HR: 3.648, 95%CI 1.057-12.595, p=0.041) and lower platelet counts (<80x10^9/L) (HR: 6.718, 95%CI 1.598-28.244, p=0.009) were identified as independent risk factors for HCC incidence.

DISCUSSION

The present study compared the different HCC suppressive effect between low genetic barrier NAs (lamivudine, adefovir, telbivudine) and a relatively higher genetic barrier agents (entecavir) for HBV-related cirrhotic patients. There was no significant difference for the incidence rate of HCC between entecavir group and control group in total cohort (p=0.525, Figure 1). To redress the imbalance of baseline characteristics (especially for follow-up duration and NAs resistance) between the two groups, a propensity score matching method was performed to eliminate the baseline difference. As a result, a sample pool consisting of 112 (56 pairs) patients was established to offset the margin of error and to deliver reliable results. The final results indicated that HCC incidence in patients treated with entecavir was significantly lower than that in patients treated with low genetic barrier drugs, which was a strong indication of the advantage of high genetic barrier agents (entecavir). Low NNT (3, 6 and 8 at years 2, 3 and 4, respectively) also revealed similar conclusions. The present study identified the following risk factors related to the incidence of HCC during NAs treatment: older age, lower platelet counts, drug resistance, and low genetic barrier agents.

Previous researchers have revealed that there is a causal link between HBV infection and development of HCC. Studies concluded a 5-year cumulative HCC incidence rate of 3.3% for chronic HBV patients, and 21.2 - 59% among cirrhotic patients before antiviral therapy were widely used.[11,12] Although antiviral therapy was found to be effective in eliminating the risk of progression and postponing the outbreak of HCC for CHB patients, incidences of HCC were still high according to results of several cohorts.[9,13-15] Risk factors of HCC identified by other studies include older age, male gender, cirrhotic status, AST, HBsAg, HBeAg, genotype C, diabetes mellitus, family history of HCC and alcohol consumption.[8,9,16-20] The present study also drew the similar conclusions as mentioned above. But

only four risk factors were got after propensity score matching. The reason might be that all of these patients were at the stage of cirrhosis, which was different from some published studies.

Do more convincing antiviral effect and higher genetic barrier deliver the same effect in terms of reducing the risk of HCC? Answers to this question have never been consistent. Kobashi *et al.* showed no significant difference in the incidence of HCC between entecavir group and lamivudine group.[7] However, the difference for follow-up duration between the two groups was a main limitation. Lim *et al.* reported that there was no significant difference in the incidence of HCC between entecavir group and lamivudine group with the method of propensity score matching in CHB patients.[8] Baseline characteristics of low genetic barrier NAs (lamivudine, adefovir, telbivudine) and high genetic barrier agents (entecavir) were comparable upon the application of propensity score matching method in the present study. Based on this, the study came to the conclusion that entecavir was more effective than low genetic barrier drugs in clinical treatment (Figure 2). This outcome was conformed to the findings of Hosaka *et al.*[4] Better yet, patients with NAs resistance in the present cohort received rescue therapy, which were not performed by Hosaka *et al.* because of historical limitations.[4,6] To enhance the accuracy of the results, the present study included treatment strategies with low genetic barrier NAs besides lamivudine. Some strategies (e.g. telbivudine, lamivudine plus adefovir) were able to deliver more effective HBV DNA suppression and/or less occurrence of resistance than lamivudine[1], which strengthened credibility of the conclusions.

Antiviral therapy is related to a virologic response and consequent reduction of hepatic necroinflammation.[21,22] A greater decrease of serum HBV DNA levels (<104 copies/mL) during patients' follow-up process indicate a lower incident HCC risk.[23,24] The authors believe that the virological breakthrough of HBV and consequent elevated alanine aminotransferase can be at least partially attributed to a higher risk of HCC during follow-up process.[6] Kurokawa *et al.* reported that an average of 5 years' treatment with lamivudine reduced the incidence of HCC in HBV-related cirrhotic patients.[25] However, 51% of included patients in this study developed YMDD mutation during follow-up process. In the present study, incidences of NAs resistance were 7.1% (4 patients) in entecavir cohort and 19.6% (11 patients) in low genetic barrier NAs cohort (p= 0.052). It was found the occurrence risk of HCC in patients with NAs resistance was 3.65 times than that in patients without drug resistance, revealing that the reduction of HCC incidence for patients with cirrhosis required NAs with higher genetic barrier. In addition, it was noticed that occurrence risk of HCC in low genetic barrier NAs cohort was 6.94 times than that in patients with

entecavir, calling for the necessity of NAs with more potent antiviral effect. Therefore, even if cirrhotic patients have achieved acceptable antiviral effect after treatment of low genetic barrier NAs, their antiviral strategies are recommended to be switched to high genetic barrier NAs.

The development of a propensity score matching system to evaluate the treatment effects for cirrhotic patients may be helpful in determining the most suitable initial treatment strategy in clinical practice. Although a relatively small number of included patients after propensity score matching, the present study represented outcomes in real-world characteristics rather than in restrictive clinical trial. The current study is featured by the specificity to cirrhosis stage, the real property of included patients and the comparable baseline characteristics, which enhance the accuracy of the results. The research highlights the effect of high genetic barrier drug (entecavir) for the decrease of HCC incidence with comparison to low genetic barrier NAs, providing evidence for the current guidelines. However, data for comparison of tenofovir and low genetic barrier NAs is still lacking and further inquires are needed in future.

CONCLUSION

In this retrospective observational study, entecavir significantly reduces the incidence of HCC comparing to low genetic barrier NAs (lamivudine, adefovir, telbivudine) for patients with HBV-related cirrhosis. Therefore, NAs with more potent antiviral activity and higher genetic barrier should be recommended strongly by clinicians, if possible, even for cirrhotic patients who have achieved acceptable antiviral effect caused by low generic barrier NAs.

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