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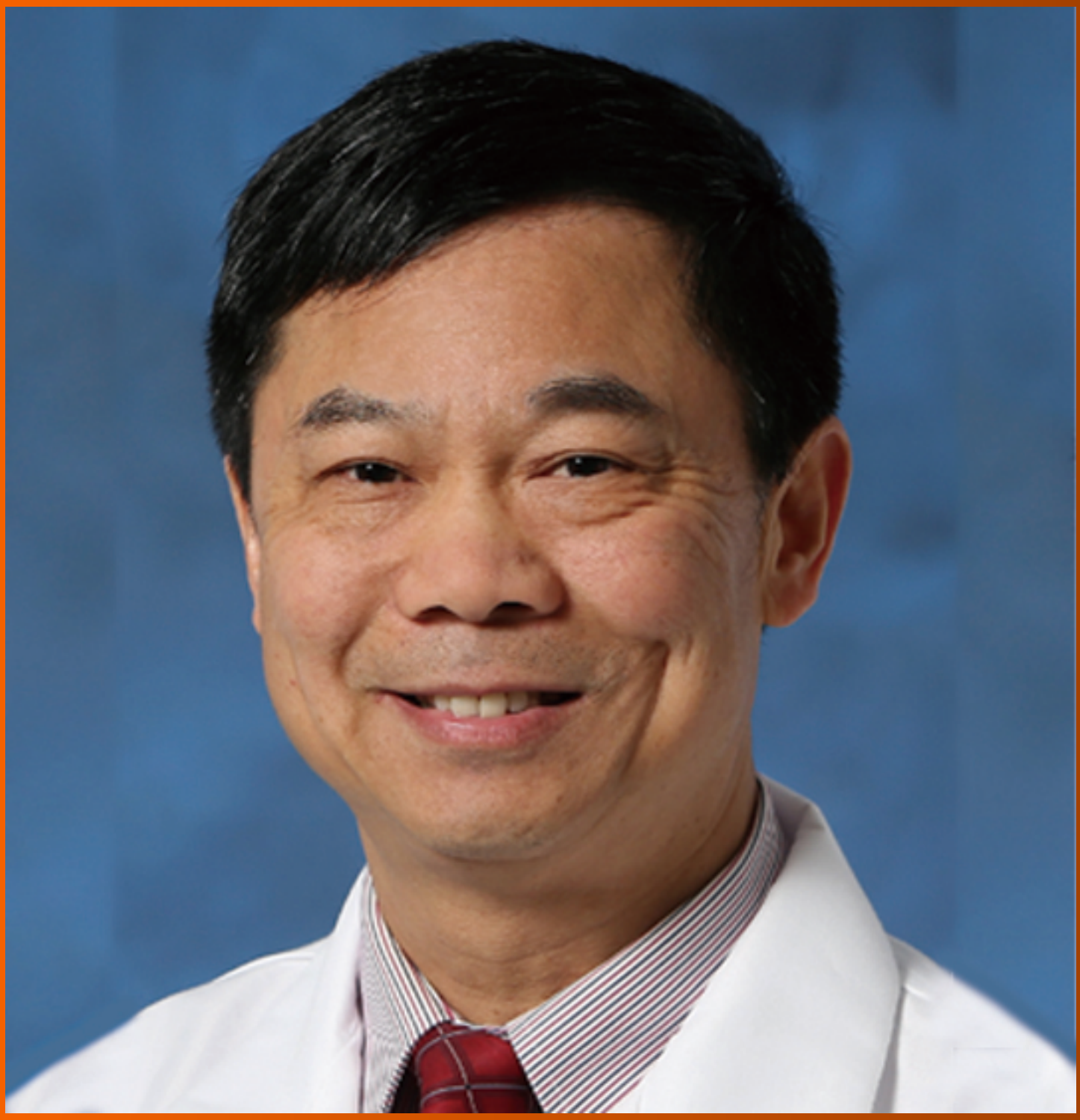

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ABOUT COVER

Editor-in-Chief of *World Journal of Hepatology*, Dr. Ke-Qin Hu is Director of Hepatology Services and Professor of Medicine in the Division of Gastroenterology and Hepatology, University of California, Irvine School of Medicine (United States). Dr. Hu's career efforts emphasize bridging research advances to bedside patient care. His clinical research has focused on the natural history and outcomes of various liver diseases and healthcare disparity. His basic science research has focused on molecular virology and diagnosis of hepatitis B and C virus infection, and chemoprevention of liver cancer. Dr. Hu has coauthored more than 150 research papers, book chapters, and review articles. He is Deputy Editor-in-Chief for Frontiers of Medicine. He is dedicated to community outreach, public health education, and reduction of healthcare disparity. (L-Editor: Filipodia)

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META-ANALYSIS

Effectiveness of entecavir in preventing hepatocellular carcinoma development is genotype-dependent in hepatitis B virus-associated liver cirrhosis

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Author contributions: Tarao K summarized the data and wrote the paper; Nozaki A, Chuma M, and Maeda S were involved in the interpretation of data, and the development and critical revision of the manuscript for important intellectual content; Taguri M conducted the statistical analysis.

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Abstract

BACKGROUND

The oral nucleos(t)ide analogue, entecavir (ETV) was demonstrated to reduce the rate of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV)-associated liver cirrhosis. However, the reduction of HCC differs in various regions of the world.

AIM

To investigate the reduction of HCC development due to ETV therapy by meta-analysis.

METHODS

We surveyed the differences in HCC development following ETV treatment based on published articles using PubMed (2004-2019).

RESULTS

The regions with the most marked reduction in HCC development due to ETV therapy were Spain (1.0%/year) and Canada (Southern part, 1.3%/year), and the most ineffective areas were South Korea (3.6%-3.8%/year), China (3.3%/year), Taiwan (2.4%-3.1%/year), and Hong Kong (2.8%/year). Following ETV administration, the incidence of HCC in genotype D regions (1.89% ± 0.28%/year,

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mean ± SE) was significantly lower than that in genotype C regions (2.91% ± 0.24%/year, $P < 0.01$). With regard to the initial HBV-DNA level, in genotype C patients (average: 5.61 Log_{10}IU/mL) this was almost the same as that in genotype D patients (average: 5.46 Log_{10}IU/mL). Moreover, there was no association between the prevalence ratio of HBV and the incidence of HCC on ETV treatment.

CONCLUSION
The effectiveness of ETV in preventing HCC development in HBV-associated liver cirrhosis is genotype-dependent.

Key Words: Hepatocellular carcinoma; Entecavir; Genotype of hepatitis B virus; Oral nucleos(t)ide analogue

Core Tip: Entecavir was demonstrated to reduce the rate of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV)-associated liver cirrhosis. The reduction of HCC differs in various regions of the world. We surveyed these differences based on published articles using PubMed (2004-2019). Following entecavir administration, the incidence of HCC in genotype D regions (1.89% ± 0.28%/year, mean ± SE) was significantly lower than that in genotype C regions (2.91% ± 0.24%/year, $P < 0.01$). The initial HBV-DNA level in genotype C patients was almost the same as that in genotype D patients. The effectiveness of entecavir in preventing HCC development in patients with HBV-associated liver cirrhosis is genotype-dependent.

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INTRODUCTION

The third-generation nucleos(t)ide analogue, entecavir (ETV) is currently recommended as one of the first-line antiviral therapies for chronic hepatitis B virus (HBV) infection. Moreover, it is generally accepted that long-term ETV treatment may reduce the incidence of hepatocellular carcinoma (HCC) in HBV-infected patients. Wong *et al*[1] demonstrated that the 5-year cumulative incidence of HCC was 13.8% in an ETV cohort *vs* 26.4% in a control cohort.

However, on surveying published reports, the effect of ETV in preventing HCC differed in various regions of the world. In this study, we examined the reduction of HCC development in various regions of the world, and the possible reasons for these differences.

MATERIALS AND METHODS

The PubMed database was searched (2004-2019) for studies published in English regarding the follow-up results of the development of HCC in patients with HBV-associated liver cirrhosis after treatment with ETV for more than 2 years. Studies with follow-up periods shorter than 3 years after ETV treatment were excluded.

In this study, we included only HBV cirrhotic cases. Furthermore, we surveyed the possible reasons for the differences in HCC reduction. We examined the association between the reduction in HCC development and initial HBV-DNA levels, which is a strong accelerating factor for HCC development[2], the prevalence of HBV in these regions, and HBV genotypes.

To compare the incidence of HCC between the main genotypes C and D, we calculated the weighted mean of the HCC incidence rate for each genotype using the

random effect model (ref: Dersimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177-188). To assess whether the incidence rate among genotype D patients was lower than that among genotype C patients, we calculated the *P* value using a *Z* test. All reported *P* values correspond to two-sided tests, and those with $P < 0.05$ were considered significant. All analyses were performed with JMP version 12 (SAS Institute, Cary, NC, United States).

RESULTS

The results of HBV-associated cirrhotic patients administered ETV are presented in Table 1.

The regions where HCC development was markedly reduced by ETV therapy were Spain (1.0%/year)[3] and Canada (Southern part) (1.3%/year)[4]. The most ineffective regions were South Korea (3.6%-3.8%/year)[5,6], China (3.3%/year)[7], Taiwan (2.4%-3.1%/year)[8,9], Japan (Ehime, southern part of Japan 2.9%/year)[10], and Hong Kong (2.8%/year)[1]. The regions with a moderate reduction were Turkey (2.2%-2.7%/year)[11,12], the Caucasus (2.2%/year)[13], and Greece (1.8%/year)[14].

With regard to the genotype of HBV, the incidence of HCC in regions where the main prevalent type is D (1.89% ± 0.28%/year, mean ± SE) was significantly lower than that in regions where the main prevalent genotype is C (2.91% ± 0.24%/year, $P < 0.01$) (Table 2).

Moreover, the incidence of HCC in regions where the main prevalent genotype is C was significantly higher than that in regions where the main prevalent genotype was other than C (D + A, 1.61% ± 0.21%/year, $P < 0.0001$).

The initial HBV-DNA levels in genotype C patients (average 5.61 Log_{10}IU/mL) was almost the same as that in genotype D patients (average 5.46 Log_{10}IU/mL) (Table 3).

The association between the prevalence ratio of HBV in various countries and the incidence of HCC with ETV treatment was as follows (Table 1): The incidence of HCC with ETV treatment with a prevalence ratio of HBV of more than 8% was 2.64% ± 0.16%/year (mean ± SE), as compared with 2.39% ± 0.14%/year in regions where the prevalence ratio of HBV was 2%-7% (not significant, $P = 0.576$).

DISCUSSION

We demonstrated that there were marked differences in the impact of ETV treatment on reducing the risk of HCC in patients with HBV-associated cirrhosis in many countries of the world. We must consider why such differences exist.

Firstly, the genotypes of HBV should be considered. Genotype C is seen mostly in Asia, and genotype A in Northwest Europe, North America, India, and Africa. Genotype D is seen in Southern Europe, Middle Eastern Europe, and India. Various cross-sectional studies have found that patients with genotype C have more severe liver disease including cirrhosis or HCC than those with other genotypes[15,16].

In cohort studies of 426 chronic hepatitis B patients from Hong Kong[17] and of 4841 HBsAg-positive men from Taiwan[18], genotype C was associated with a 3-to 5-fold increased risk of HCC, respectively, compared with other HBV genotypes. Moreover, it was reported that the estimated 5-year cumulative incidence of HCC was 17% in East Asia where HBV genotype C is predominant and 10% in Western regions where HBV genotype D or A is predominant[19].

It is considered that the same tendency exists even on long-term treatment with ETV, and the incidence of HCC is higher in genotype C regions than in regions with other genotypes (especially genotype D).

In our studies, we demonstrated that ETV treatment of HBV cirrhotic patients with genotype C was less effective at preventing the occurrence of HCC than in those with other genotypes (chiefly genotype D).

In support of our findings, Kao *et al*[20] demonstrated differences in the response to lamivudine between HBV genotypes. They reported that genotype B showed a better virological response to lamivudine than genotype C in Taiwan.

Another factor that must be taken into account is the association between the prevalence ratio of HBV in various places and the incidence of HCC under ETV treatment. The incidence of HCC under ETV treatment where the prevalence ratio of HBV is more than 8% was 2.64% ± 0.16%/year, as compared with 2.39% ± 0.14%/year in regions where the prevalence ratio of HBV was 2%-7% (not significant, $P = 0.576$).

Another important factor that must be taken into consideration is the initial HBV-

Table 1 Difference in the impact of entecavir treatment on the risk of hepatocellular carcinoma in patients with hepatitis B virus-associated cirrhosis in various regions of the world

Ref.	Region	Main genotype	Prevalence ratio	Entecavir administered to HBV cirrhotics patients	Observation period (yr)	Incidence of HCC (%/yr)
Riveiro-Barciela *et al*[3]	Spain (Caucasian)	D	2%-7%	64	4.6	1.0
Coffin *et al*[4]	Canada (South)	D	< 2%	25	3.2	1.3
Hosaka *et al*[21]	Japan (Tokyo)	C	< 2%	79	5.0	1.4
Papatheodoridis *et al*[14]	Greece	A	2%-7%	69	3.3	1.8
Idilman *et al*[11]	Turkey	D	2%-7%	72	4.0	2.2
Arends *et al*[13]	Caucasus	D	> 8%	155	3.5	2.2
Su *et al*[8]	Taiwan	C	> 8%	1315	4.0	2.4
Köklü *et al*[12]	Turkey	D	2%-7%	73	3.0	2.7
Wong *et al*[1]	Hong Kong	C	> 8%	482	5.0	2.8
Watanabe *et al*[10]	Japan (Ehime)	C	2%-7%	86	5.0	2.9
Chen *et al*[9]	Taiwan	C	> 8%	586	4.9	3.1
Chen *et al*[2]	China (Chinese)	C	> 8%	61	4.0	3.3
Kim *et al*[5]	Korea	C	2%-7%	367	5.0	3.6
Choi *et al*[6]	Korea	C	2%-7%	510	4.0	3.8

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

Table 2 Difference in the incidence of hepatocellular carcinoma under long-term treatment with entecavir between genotype C and genotype D cirrhotic patients

	Incidence of HCC (%/yr)	*P* value
Genotype C group (n = 8)	2.91 ± 0.24 (SE)	$P < 0.01$
Genotype D group (n = 5)	1.89 ± 0.28 (SE)	$P < 0.01$

HCC: Hepatocellular carcinoma.

DNA level. However, we demonstrated that the initial HBV-DNA level in genotype C patients was almost the same as that in genotype D patients.

CONCLUSION

The impact of long-term ETV treatment on reducing the risk of HCC in patients with HBV cirrhosis differs in many countries of the world[1-13,21]. Moreover, it was demonstrated that effectiveness of ETV in preventing HCC development is genotype-dependent in HBV-associated liver cirrhosis.

Table 3 Comparison of initial hepatitis B virus deoxyribonucleic acid levels (log_{10} IU/mL) between genotype C and D cirrhotic patients treated with entecavir

Main genotype	Ref.	Entecavir administered to HBV cirrhotic patientssis	Initial HBV DNA	Average
C	Su *et al*[8]	1315	5.5	5.61
C	Wong *et al*[1]	482	5.0	
C	Watanabe *et al*[10]	86	6.4	
C	Chen *et al*[9]	586	5.9	
C	Chen *et al*[2]	61	5.8	
C	Kim *et al*[5]	367	4.6	
C	Choi *et al*[6]	510	6.7	
D	Riveiro-Barciela *et al*[3]	64	4.9	5.46
D	Coffin *et al*[4]	25	6.5	
D	Idilman *et al*[11]	72	5.5	
D	Arends *et al*[13]	155	5.4	
D	Köklü *et al*[12]	73	5.7	

HBV DNA: Hepatitis B virus deoxyribonucleic acid.

ARTICLE HIGHLIGHTS

Research background

The oral nucleos(t)ide analogue, entecavir (ETV) was demonstrated to reduce the rate of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV)-associated liver cirrhosis. However, the reduction in HCC is different in various countries of the world.

Research motivation

The relationship between the reduction of HCC and HBV genotypes is interesting.

Research objectives

We surveyed the differences in the reduction of HCC development following ETV administration in many countries.

Research methods

We surveyed the differences in the reduction of HCC development following long-term administration of ETV based on already published articles using PubMed (2004-2019).

Research results

The countries which showed the greatest reduction in HCC development following ETV administration were Spain, Canada, and most ineffective countries or regions were South Korea, China, Taiwan, and Hong Kong. With ETV administration, the incidence of HCC in genotype D regions was significantly lower than that in genotype C regions. The initial HBV-DNA levels in genotype C patients was almost the same as that in genotype D patients. No relationship was observed between the prevalence ratio of HBV and the incidence of HCC following ETV treatment.

Research conclusions

The effectiveness of ETV in preventing HCC development in HBV-associated liver cirrhosis is genotype-dependent.

Research perspectives

In countries with low effectiveness of ETV in the prevention of HCC development, frequent surveillance using imaging modalities will be necessary.

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