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

Kazuo Tarao, Akito Nozaki, Makoto Chuma, Masataka Taguri, Shin Maeda

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,
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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

**Citation:** Tarao K, Nozaki A, Chuma M, Taguri M, Maeda S. Effectiveness of entecavir in preventing hepatocellular carcinoma development is genotype-dependent in hepatitis B virus-associated liver cirrhosis. *World J Hepatol* 2021; 13(1): 144-150

**URL:** https://www.wjgnet.com/1948-5182/full/v13/i1/144.htm

**DOI:** https://dx.doi.org/10.4254/wjh.v13.i1.144

**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)\(^5\), China (3.3%/year)\(^6\), Taiwan (2.4%-3.1%/year)\(^7\), Japan (Ehime, southern part of Japan 2.9%/year)\(^8\), and Hong Kong (2.8%/year)\(^9\). The regions with a moderate reduction were Turkey (2.2%-2.7%/year)\(^10,11,12\), 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 (HBV cirrhosis patients) | Observation period (yr) | Incidence of HCC (%/yr) |
|--------------------|-------------------------------|---------------|-------------------------------------------|-------------------------|-------------------------|
| Riveiro-Barcia 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[5]    | Japan (Tokyo)                 | C             | < 2%                                      | 79                      | 5.0                     | 1.4                     |
| Papatheodoridis et al[6] | Greece                      | A             | 2%-7%                                     | 69                      | 3.3                     | 1.8                     |
| Idilman et al[7]   | Turkey                        | D             | 2%-7%                                     | 72                      | 4.0                     | 2.2                     |
| Arends et al[8]    | Caucasus                      | D             | > 8%                                      | 155                     | 3.5                     | 2.2                     |
| Su et al[9]        | Taiwan                        | C             | > 8%                                      | 1315                    | 4.0                     | 2.4                     |
| Kökdü et al[10]    | Turkey                        | D             | 2%-7%                                     | 73                      | 3.0                     | 2.7                     |
| Wong et al[11]     | Hong Kong                     | C             | > 8%                                      | 482                     | 5.0                     | 2.8                     |
| Watanabe et al[12] | Japan (Ehime)                 | C             | 2%-7%                                     | 86                      | 5.0                     | 2.9                     |
| Chen et al[13]     | Taiwan                        | C             | > 8%                                      | 586                     | 4.9                     | 3.1                     |
| Chen et al[14]     | China (Chinese)               | C             | > 8%                                      | 61                      | 4.0                     | 3.3                     |
| Kim et al[15]      | Korea                         | C             | 2%-7%                                     | 367                     | 5.0                     | 3.6                     |
| Choi et al[16]     | 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

| Genotype group | 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]. 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 patients | 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[9] | 86 | 6.4 | |
| C             | Chen et al[10] | 586 | 5.9 | |
| C             | Chen et al[11] | 61 | 5.8 | |
| C             | Kim et al[12] | 367 | 4.6 | |
| C             | Choi et al[13] | 510 | 6.7 | |
| D             | Riveiro-Barciela et al[14] | 64 | 4.9 | 5.46 |
| D             | Coffin et al[15] | 25 | 6.5 | |
| D             | Idilman et al[16] | 72 | 5.5 | |
| D             | Arends et al[17] | 155 | 5.4 | |
| D             | Köklü et al[18] | 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.
REFERENCES

1 Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, Ju HW, Leung JM, Lai JW, Lo AO, Chan HY, Wong VW. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 2013; 58: 1537-1547 [PMID: 23389810 DOI: 10.1002/hep.26301]

2 Chen CJ, Yang HI, Su J, Jen CL, Yu SL, Lu SN, Huang GT, Iioeje UH. REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]

3 Rivero-Barciela M, Tabernerio D, Calleja JL, Lens S, Manzano ML, Rodriguez FG, Crespo J, Paparras B, Pascasio JM, Comas C, Gutierrez ML, Aguñre A, Suarez E, Garcia-Sananiego J, Rivero M, Acero D, Fernandez-Bermejo M, Moreno D, Sanchez-Poblete P, de Cuencsa B, Moreno-Palomares JJ, Esteban R, Buiti M. 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 [PMID: 28078526 DOI: 10.1007/s10620-017-4448-7]

4 Coffin CS, Rezaeeaval M, Pang JX, Alcantara L, Klein P, Burak KW, Myers RP. The incidence of hepatocellular carcinoma is reduced in patients with chronic hepatitis B on long-term nucleos(t)ide analogue therapy. *Aliment Pharmacol Ther* 2014; 40: 1262-1269 [PMID: 25312649 DOI: 10.1111/apt.12990]

5 Kim HS, Kim BK, Kim SU, Park JY, Kim DY, Song KJ, Park JW, Kim YJ, Baatarkhuu O, Han KH, Ahn SH. Association Between Level of Fibrosis, Rather Than Antiviral Regimen, and Outcomes of Patients With Chronic Hepatitis B. *Clin Gastroenterol Hepatol* 2016; 14: 1647-1656.e6 [PMID: 27305847 DOI: 10.1016/j.cgh.2015.05.039]

6 Choi J, Kim HJ, Lee J, Cho S, Ko MJ, Lim YS. Risk of Hepatocellular Carcinoma in Patients Treated with Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study. *JAMA Oncol* 2019; 5: 30-36 [PMID: 30627080 DOI: 10.1001/jamaoncol.2018.4070]

7 Tsuzuki S, Orita H, Sato N. Intermolecular interactions of oligothioanecoenes. Do S: S interactions positively contribute to crystal structures of sulfur-containing aromatic molecules? *J Chem Phys* 2016; 145: 174503 [PMID: 27825222 DOI: 10.1063/1.4965850]

8 Su TH, Hu TH, Chen CY, Huang YH, Chuang WL, Lin CC, Wang CC, Su WW, Chen MY, Peng CY, Chien RN, Huang YW, Wang HY, Lin CL, Yang SS, Chen TM, Mo LR, Hsu SJ, Tseng KC, Hsieh TY, Suk FM, Hu CT, Bair MJ, Liang CC, Lei YC, Tsen TC, Chen CL, Kao JH; C-TEAM study group and the Taiwan Liver Diseases Consortium. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int* 2016; 36: 1755-1764 [PMID: 27634134 DOI: 10.1111/liv.13253]

9 Chen YC, Peng CY, Jeng WJ, Chien RN, Liaw YF. Clinical outcomes after interruption of entecavir therapy in HBsAg-negative chronic hepatitis B patients with compensated cirrhosis. *Aliment Pharmacol Ther* 2015; 42: 1182-1191 [PMID: 26381928 DOI: 10.1111/apt.13409]

10 Watanabe T, Tokumoto Y, Joko K, Michitaka K, Mashiba T, Hiraoka A, Ochi H, Koizumi Y, Tada F, Hiraoka M, Yoshida O, Imay Y, Abe M, Hiasa Y. Effects of long-term entecavir treatment on the incidence of hepatocellular carcinoma in chronic hepatitis B patients. *Hepatology* 2016; 50: 30-327 [PMID: 26198757 DOI: 10.1002/1170-9647-8]

11 Idilman R, Gunsar F, Koruk M, Keskin O, Meral CE, Gulsen M, Elhan AH, Akarca US, Yurdaydin C. Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naive chronic hepatitis B patients in the real-world setting. *J Viral Hepat* 2015; 22: 504-510 [PMID: 25431108 DOI: 10.1111/jhj.12359]

12 Kökkü S, Tuna Y, Gülşen MT, Demir M, Köksal AS, Koçkar MC, Aygün C, Coban S, Ozdil K, Ataseven H, Akin E, Pürnak T, Yüksel I, Ataseven H, Ibiş M, Yildirim B, Nadir I, Kılıçkuzman M, Akbal E, Yüksel O, Başar O, Alkan E, Baykal O. 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 [PMID: 23063679 DOI: 10.1016/j.cgh.2012.10.003]

13 Arends P, Sonneveld MJ, Zoutendijk R, Carey I, Brown A, Fasano M, Dettering K, Reijnders JG, Oo Y, Petersen J, van Bommel F, de Knegt RJ, Santantonio T, Berg T, Welzel TM, Arends P. Risk of hepatocellular carcinoma in chronic hepatitis B patients: limited role for risk scores in Caucasians. *Gastro* 2015; 64: 1289-1295 [PMID: 25011935 DOI: 10.11136/gutjnl-2014-307023]

14 Papatheodoridis GV, Manolakopoulos T, Touloumi G, Nikolopoulos G, Raptopoulou-Gigi M, Gogos C, Vafadakis-Zaoublis I, Karamanolis D, Chouta A, Iliaas A, Drakoulis C, Minidis K, Ketikoglou I, Manesis E, Mela M, Hatzis G, Dalekos GN; HepNet. Greece Study Group. Hepatocellular carcinoma risk in HBsAg-negative chronic hepatitis B patients with or without cirrhosis treated with entecavir: HepNet Greece cohort. *J Viral Hepat* 2015; 22: 120-127 [PMID: 25040685 DOI: 10.1111/jhj.12283]

15 Kim BK, Revill PA, Ahn SH. HBV genotypes: relevance to natural history, pathogenesis and treatment of chronic hepatitis B. *Antivir Ther* 2011; 16: 1169-1186 [PMID: 22155900 DOI: 10.3851/IMP1982]

16 Kramvis A, Kew MC. Relationship of genotypes of hepatitis B virus to mutations, disease progression and response to antiviral therapy. *J Viral Hepat* 2005; 12: 456-464 [PMID: 16108759 DOI: 10.1111/j.1365-2893.2005.00624.x]

17 Chan HL, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, Sung JJ. Genotype C hepatitis B virus
infection is associated with an increased risk of hepatocellular carcinoma. *Gut* 2004; **53**: 1494-1498 [PMID: 15361502 DOI: 10.1136/gut.2003.033324]

18 **Yu MW**, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**: 265-272 [PMID: 15713961 DOI: 10.1093/jnci/dji043]

19 **Fattovich G**, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335-352 [PMID: 18096267 DOI: 10.1016/j.jhep.2007.11.011]

20 **Kao JH**, Liu CJ, Chen DS. Hepatitis B viral genotypes and lamivudine resistance. *J Hepatol* 2002; **36**: 303-304 [PMID: 11830346 DOI: 10.1016/s0168-8278(01)00246-x]

21 **Hosaka T**, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saiyoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; **58**: 98-107 [PMID: 23213040 DOI: 10.1002/hep.26180]
