Comparative Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Receiving Tenofovir- or Entecavir-Based Regimens: A Meta-Analysis Using Individual Patient Data

Abstract No. 115

Won-Mook Choi[1], Terry Cheuk-Fung Yip[2], GraceWong[2], W. Ray Kim[3], Jacques Yu[4], Leland Yee[4], Craig Brooks-Rooney[5], Tristan Curteis6, Harriet Cant[6], Chien-Hung Chen[7], Chi-Yi Chen[8], Yi-Hsiang Huang[9,10], Young-Joo Jin[11], Dae Won Jun[12], Jin-Wook Kim[13,14], Neung Hwa Park[15,16], Cheng-Yuan Peng[17,18], Hyun Phil Shin19, Jungwoo Shin[15], Yao-Hsu Yang[20,21], Young-Suk Lim[1]

[1]University of Ulsan College of Medicine, Department of Gastroenterology, Liver Center, Asan Medical Center, Seoul, Korea, Rep. of South; [2]The Chinese University of Hong Kong, CUHK Medical Data Analytics Centre, Department of Medicine and Therapeutics, Hong Kong SAR, Hong Kong; [3]Stanford University School of Medicine, Division of Gastroenterology and Hepatology, Stanford, United States; [4]Gilead Sciences, Foster City, United States; [5]Costello Medical Consulting Ltd, United States; [6]Costello Medical Consulting Ltd, Cambridge, United Kingdom; [7]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine Kaohsiung, Division of Hepatogastroenterology, Department of Internal Medicine, Taiwan; [8]Ditmanson Medical Foundation Chia-Yi Christian Hospital Chia-Yi, Division of Hepatogastroenterology, Department of Internal Medicine; [9]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [10]National Yang Ming Chiao Tung University, Institute of Clinical Medicine, Taipei, Taiwan; [11]Digestive Disease Center, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, Korea, Rep. of South; [12]Hanyang University College of Medicine, Department of Internal Medicine, Hanyang University Hospital, Seongnam, United States; [13]Seoul National University Bundang Hospital, Department of Medicine, Seongnam, Korea, Rep. of South; [14]Seoul National University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [15]Ulsan University Hospital, Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan, Korea, Rep. of South; [16]Ulsan University Hospital, Biomedical Research Center, University of Ulsan College of Medicine, Ulsan, Korea, Rep. of South; [17]China Medical University Hospital, Center for Digestive Medicine, Department of Internal Medicine, Taichung, Taiwan; [18]China Medical University, School of Medicine, Taichung, Taiwan; [19]Kyung Hee University School of Medicine, Department of Gastroenterology and Hepatology, Kyung Hee University Hospital at Gangdong, Seoul, Korea, Rep. of South; [20]Chiayi Chang Gung MemoriaIn Hospital, Department of Traditional Chinese Medicine, Chiayi, Taiwan; [21]Chang Gung Memorial Hospital, Health Information and Epidemiology Laboratory, Chiayi, Taiwan

Conclusions

Patients with CHB receiving treatment with TDF were significantly less likely to develop HCC than those receiving ETV.

Although statistical significance varied, TDF was consistently associated with lower HCC risk throughout all sensitivity and subgroup analyses, notably in HBeAg positive patients.

These findings should be considered when determining the most appropriate treatment course for CHB patients and have implications for healthcare systems in reducing the burden of the long-term consequences of CHB.

References: 1. Gomaa AI, et al. World J Gastroenterol 2008;14(27):4300–8; 2. Llovet JM, et al. Lancet 2003;362(9399):1907–17; 3. Terrault NA, et al. Hepatology 2018;67(4):1560–99; 4. Choi WM, et al. J Hepatol 2022;76(1):186–94.

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; dL, deciliter; ETV, entecavir; F, female; g, gram; HBeAg, hepatitis B e-antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalised ratio; IPD, individual patient data; IQR, interquartile range; IU, international unit; mL, milliliter; µL, microliter;
PSM, propensity score matching; PSW, propensity score weighting; TDF, tenofovir disoproxil fumarate.

Disclosures: WMC, CHC, CYC, YJJ, DWJ, JWK, NHP, HPS, JWS, YHY: No conflicts of interest to disclose. TCFY: advisory committee member and speaker for Gilead Sciences. GLHW: advisory committee member for Gilead Sciences and Janssen, speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche, received research grants from Gilead. WRK: advisory committee member for Gilead Sciences, Inovio Pharmaceuticals and Roche. LJY: employee of, and owns stock in, Gilead Sciences. CBR, TC: employees of Costello Medical, which received payment from Gilead Sciences for analytical services for this study. HC: was an employee of Costello Medical at the time of the study. YHH: received research grants from Gilead Sciences and Bristol-Meyers Squibb and honoraria from Abbvie, Gilead Sciences, Bristol-Meyers Squibb, Ono Pharmaceutical, Merck Sharp & Dohme, Eisai, Eli Lilly, Ipsen and Roche and has served in an advisory role for Abbvie, Gilead Sciences, Bristol-Meyers Squibb, Ono Pharmaceuticals,Eisai, Eli Lilly, Ipsen, Merck Sharp & Dohme and Roche. CYP: advisory committee member for Bristol-Myers Squibb and Gilead Sciences. YSL: advisory board member of AbbVie, Arbutus Biopharma, Assembly Biosciences, Brii Biosciences, Bayer Healthcare, GlaxoSmithKline, Gilead Sciences, Janssen, Olix Pharmaceuticals, Roche, Vaccitech, and Vir Biotechnology; and received grant/research support from Gilead Sciences.

Acknowledgments: The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Ben Farrar, PhD, Elliot Dryer-Beers, PhD, Laura Clark, DPhil, Radost Pencheva, MSc, and Seth Francis-Graham, PhD, from Costello Medical, UK, and Zarena Jafry, MPH, from Costello Medical, US, for statistical and data management support, and Isabel Haber, BS, from Costello Medical, US, for medical writing and editorial assistance based on the authors' input and direction.

Background

- Chronic hepatitis B (CHB) is a major risk factor for hepatocellular carcinoma (HCC), the most common primary liver cancer and third leading cause of cancer-related death;[1,2] it is crucial to identify CHB therapies effective at reducing HCC risk.
- Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are recommended as first-line treatments for CHB.[3]
- Previous aggregate data meta-analyses have been unable to reach a consensus regarding the relative effectiveness of TDF and ETV in reducing HCC risk, due to challenges with heterogeneity and differing methodologies of included studies.[4]
- The use of individual patient data (IPD) rather than aggregate data allows for a more consistent analytic approach across multiple study sites and reduces heterogeneity.[4]

Objective

- To compare HCC risk using IPD from CHB patients receiving treatment with TDF or ETV and identify any subgroups who particularly benefit from either treatment.

Methods

- A literature review identified 20 observational studies from East Asia reporting HCC incidence in patients receiving TDF or ETV; 11 studies agreed to contribute IPD.
- Key patient eligibility criteria:
  - Treatment-naïve adults with CHB
  - Completed at least one year of treatment with TDF or ETV monotherapy
- Primary analysis
  - One-stage IPD meta-analysis evaluated the hazard ratio (HR) of treatment with TDF versus ETV to reduce HCC risk using a multivariable Cox proportional hazards model.
  - Adjustment for potential confounding variables (treatment, age, sex, viral load, hepatitis B eantigen [HBeAg], cirrhosis, decompensated cirrhosis, alanine aminotransferase [ALT], diabetes, bilirubin, hypertension, creatinine, alpha fetoprotein [AFP], albumin, international normalised ratio [INR], ascites, hepatic encephalopathy, platelet count) and multiple imputation to account for missing data were performed.
- Secondary analyses
  - Sensitivity analyses assessed the robustness of the primary results under different methodological assumptions and approaches.
  - Subgroup analyses compared HCC risk with TDF and ETV in subgroups of clinical interest (age, sex, HBeAg positivity, cirrhosis status, diabetes status).

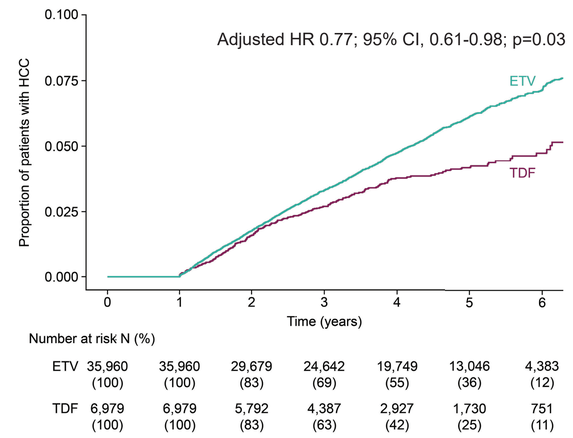
Results

Table 1. Patient disposition and baseline characteristics

Characteristic	TDF (n=6,979)	ETV (n=35,960)
Age, median (IQR), years	48.32 (12.21)	52.26 (12.60)
Sex (%)	F: 38.64	F: 34.13
Viral load, median (IQR), log_{10} IU/mL	5.76 (2.00)	5.47 (2.04)
HBeAg positivity (%)	49.65	33.69
Cirrhosis (%)	38.01	39.23
Albumin, median (IQR), g/dL	4.11 (0.72)	4.02 (0.64)
Platelet count, median (IQR), x1,000/µL	180.92 (66.51)	178.47 (70.25)
Follow-up time (median [IQR], years)	3.71 (1.58)	3.97 (1.62)

Results

Figure 1. Cumulative incidence of HCC in patients with CHB treated with TDF or ETV



Adjustment was performed for the following variables: treatment, age, sex, viral load, HBeAg, cirrhosis, decompensated cirrhosis, ALT, diabetes, bilirubin, hypertension, creatinine, AFP, albumin, INR, ascites, hepatic encephalopathy and platelet count.

- Patients receiving TDF had a significantly lower risk of HCC than those receiving ETV (Figure 1).
  - Risk of HCC diverged between the groups after 2.5 years of follow-up.

Table 2. Sensitivity analyses comparing the risk of HCC between TDF and ETV

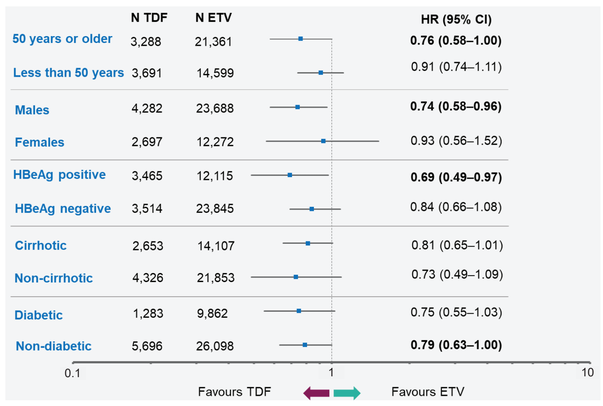
Analysis	N	HR (95% CI)	p-value
Propensity score matching (PSM)[a]	TDF: 6,475 ETV: 15,958	0.73 (0.59–0.88) 1 (reference)	<0.01
Propensity score weighting (PSW)[b]	TDF: 6,220 ETV: 14,488	0.83 (0.67–1.03) 1 (reference)	0.10
Alternative cirrhosis definition[c]	TDF: 6,979 ETV: 35,960	0.77 (0.61–0.98) 1 (reference)	0.03
Complete cased	TDF: 6,116 ETV: 31,988	0.82 (0.64–1.04) 1 (reference)	0.10
Treatment start date[e]	TDF: 6,922 ETV: 26,498	0.83 (0.66–1.05) 1 (reference)	0.11

[a]Matched patients 1:5 (TDF:ETV) to balance characteristics across treatment arms; effective sample size is presented
[b]Balanced the observed baseline characteristics in both treatment arms; effective sample size is presented
[c]Used platelet count threshold <100,000/µL within the composite cirrhosis definition (versus <150,000/µL in the primary analysis)
[d]Excluded patients missing data for any mPAGE-B variables (age, gender, platelet count, albumin)
[e]Excluded patients initiating treatment prior to 2011

- Regardless of analytic methodology, TDF was associated with consistently lower risk of HCC than ETV (Table 2).

Figure 2. Subgroup analyses for cumulative incidence of HCC in patients with CHB treated with TDF or ETV

- Regardless of analytic methodology, TDF was associated with a consistently lower risk of HCC than ETV (Table 2).



Statistically significant results are in bold. For the '50 years or older' and 'non-diabetic' subgroups, the upper bound of each CI is < 1.00, but each has been rounded up to 1.00 when reported to two decimal places.

- TDF was associated with a lower risk of HCC than ETV in all subgroup (Figure 2).
  - Risk difference was statistically significant for the ≥50 years of age (p<0.05), male (p=0.02), HBeAg positive (p=0.03) and nondiabetic subgroups (p<0.05) and was most pronounced in the HBeAg positive subgroup.