Tenofovir may be superior to entecavir for preventing hepatocellular carcinoma and mortality in individuals chronically infected with HBV: a meta-analysis

Many studies have demonstrated that monotherapy with tenofovir disoproxil fumarate (TDF) or entecavir (ETV) can reduce the risk of liver complications in individuals chronically infected with HBV (CHB). Unclear is whether one monotherapy is more effective than the other at preventing these outcomes. In a recent issue of this journal, Lee and coworkers[1] reported data from a large population of treatment-naive CHB patients in which risk of hepatocellular carcinoma (HCC), all-cause mortality or liver transplantation was similar with either monotherapy. Similar results were observed in subgroups of patients with chronic hepatitis or cirrhosis. While this study involved more than 7000 South Korean patients who were enrolled during more than a decade and whose virological and biochemical data over several years were analysed, its findings must be treated with caution because the two groups differed substantially in median treatment duration (TDF since December 2012, ETV before December 2012) and median follow-up (36.4 vs 60 months), both of which affect risk of the outcomes measured by Lee *et al*. Unfortunately, the authors did not take these differences into account during propensity score matching (PSM) or inverse probabilistic treatment weighting.

We searched PubMed, EMBASE and Web of Science for cohort studies comparing TDF or ETV monotherapy for the ability to prevent the three outcomes measured by Lee *et al* in previously treatment-naive CHB patients. To be included in our meta-analysis, studies had to report the sample size as well as sufficient data to calculate risk ratios (RRs) and 95% CIs. We identified 10 studies analysing 11 cohorts of 19 849 patients who received TDF and 50 712 who received ETV (table 1).[1–10] Nearly all patients (98%) were from Asia and all but one cohort[10] was from a hospital. Follow-up lasted 20.3–60.0 months in the TDF group and 24.0–69.9 months in the ETV group. Among all patients, HCC occurred in 639 of TDF patients (3.22%) and 2713 of ETV patients (5.35%); all-cause mortality or liver transplantation occurred in 299 (1.70%) and 443 (2.59%) of the respective groups. Similar results were observed after PSM. TDF was associated with significantly lower HCC incidence than ETV, either before PSM (RR 0.49, 95% CI 0.38 to 0.64, p<0.001) or after (RR 0.53, 95% CI 0.38 to 0.73, p<0.001). TDF was also associated with significantly lower incidence of all-cause mortality or liver transplantation, either before PSM (RR 0.66, 95% CI 0.57 to 0.76, p<0.001)

Table 1 Characteristic and outcomes of tenofovir and entecavir monotherapy for chronic HBV

Study	Country/ region	Enrolment period	Drugs	Sample size	Age, years, median or mean	HBV DNA, log_{10} IU/mL	HBeAg (+), %	Cirrhosis, %	Follow-up, months	Treatment duration, months	Outcomes, p-value	
											HCC	Death or liver transplantation
Cheuk-Fung Yip *et al* 2019[4]	Hong Kong	2008–2018	Tenofovir	1309	43.2	4.9	55.1	2.9	33.6	–	<0.001	–
			Entecavir	28 041	53.4	5.3	29.7	13.6	44.4	–		
Choi *et al* 2018a[10]	Korea	2012–2014	Tenofovir	12 692	48.6	>2000 IU/mL	–	27.5	36	37	<0.001	0.22
			Entecavir	11 464	49.3		–	26.1	51	51		
Choi *et al* 2018b[10]	Korea	2010–2016	Tenofovir	1141	48.1	6.4	56.2	57.2	32.0	–	0.03	0.33
			Entecavir	1560	49.2	6.7	54.7	59.9	48.0	–		
Goyal *et al* 2015[6]	India	2007–2014	Tenofovir	220	47.3	5.5	38.6	100	45	45	>0.05	0.65
			Entecavir	180	48.1	5.7	38.8	100	36	36		
Hsu *et al* 2019[2]	Six countries or regions	?–2018	Tenofovir	700	45.7	5.00	33.7	18.7	60	–	0.005	–
			Entecavir	4837	50.8	5.5	33.0	27.8	38.7	–		
Kim *et al* 2019[9]	Korea	2007–2017	Tenofovir	604	50	6.0	62.3	44.2	33	33	0.340	0.955
			Entecavir	721	52	6.4	59.7	48.0	66	66		
Kim *et al* 2019[8]	Korea	2012–2014	Tenofovir	1413	48.8	5.4	49.1	29.1	–	–	0.516	0.981
			Entecavir	1484	48.2	5.7	51.1	33.6	–	–		
Köklü *et al* 2013[3]	Turkey	2005–2012	Tenofovir	72	54.2	5.6	12.5	100	21.4	21.5	0.46	0.87
			Entecavir	77	52.4	5.7	22.1	100	24.0	23.9		
Lee, *et al* 2019[1]	Korea	2007–2018	Tenofovir	1439	47.3	6.4	57.2	33.6	36.4	–	0.613	0.853
			Entecavir	1583	46.7	6.5	61.5	35.8	60.0	–		
Tsai, *et al* 2017[7]	Taiwan	2007–2013	Tenofovir	83	54.9	6.4	23	100	20.3	–	0.15	–
			Entecavir	359	57.8	6.3	23	100	43.8	–		
Yu, *et al* 2018[5]	Korea	2007–2015	Tenofovir	176	49.0	4.5	59.1	43.8	33.6	–	0.471	–
			Entecavir	406	53.0	6.7	52.2	36.5	69.9	–		

HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma.

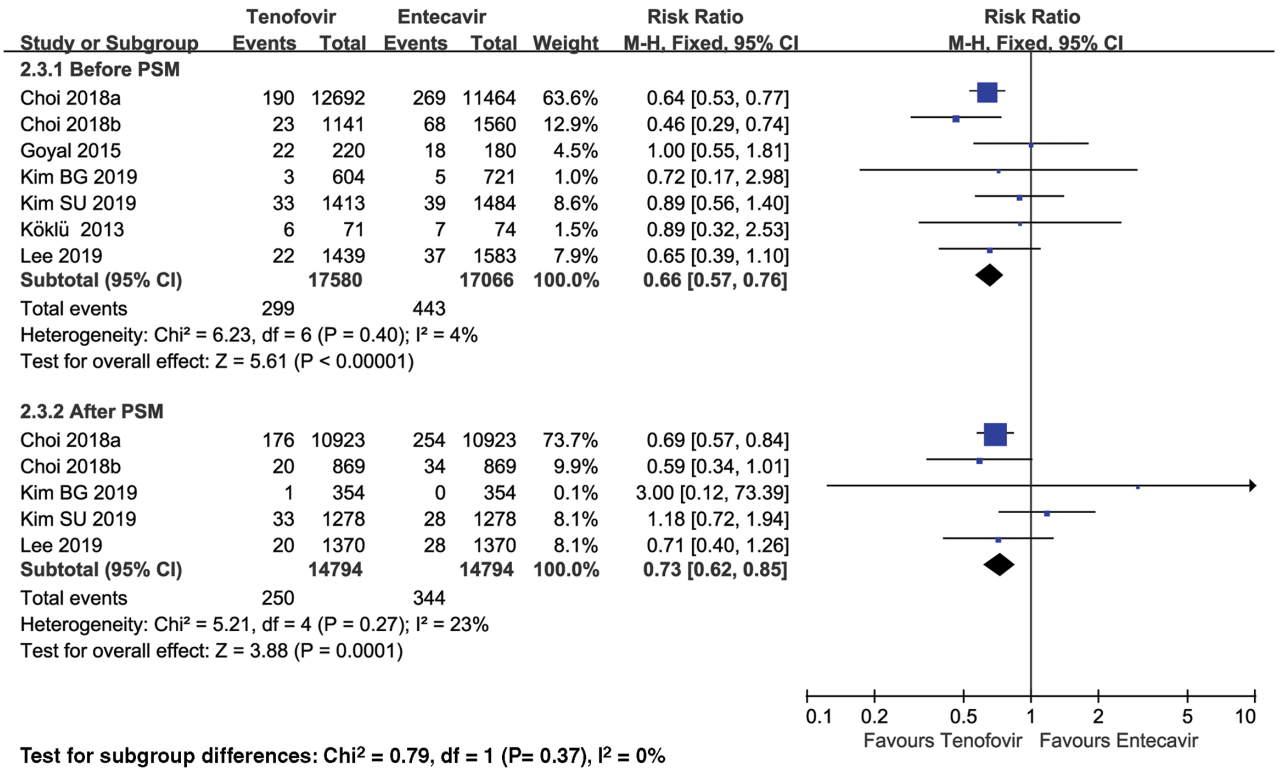

Figure 1 Forest plot of incidence of mortality or liver transplantation between tenofovir group and entecavir group. PSM, propensity score matching.

or after (RR 0.73, 95% CI 0.62 to 0.85, p<0.001) (figure 1). Similar results were obtained with fixed- or random-effect meta-analysis models, and when the meta-analysis was repeated after excluding each study one by one.

Our meta-analysis suggests that the findings of Lee *et al* may not accurately reflect the broader evidence base, which seems to indicate that TDF may be superior to ETV as monotherapy for reducing risk of HCC, all-cause mortality and liver transplantation in CHB patients. Our findings should be applied carefully because patients in each monotherapy group were followed up for substantially different periods, and we did not meta-analyse numerous studies that reported incomplete data. Moreover, our meta-analyses may be biased by the quality of data collected in the included studies.

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