Original Article

Tenofovir Alafenamide Fumarate, Tenofovir Disoproxil Fumarate and Entecavir: Which is the Most Effective Drug for Chronic Hepatitis B? A Systematic Review and Meta-analysis

Xuefeng Ma[1#], Shousheng Liu[2,3#], Mengke Wang[1], Yifen Wang[1], Shuixian Du[1], Yongning Xin[1,3*] and Shiying Xuan[1,3*]

[1]Department of Infectious Disease, Qingdao Municipal Hospital, Qingdao University, Qingdao, Shandong, China; [2]Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, Shandong, China; [3]Digestive Disease Key Laboratory of Qingdao, Qingdao, Shandong, China

Abstract

Background and Aims: The therapeutic effect of tenofovir alafenamide fumarate (TAF), tenofovir disoproxil fumarate (TDF) and entecavir (ETV) on chronic hepatitis B (CHB) patients remains inconsistent. The aim of this study was to explore the differences in virological responses to TAF, TDF and ETV in patients with CHB. ***Methods:*** Literature searches were conducted of the PubMed, EMBASE, and the Cochrane Library databases to identify randomized controlled trials and observational studies published up to July 21, 2020. Statistical comparisons of virological response between TDF, ETV, and TAF were carried out with pooled odds ratio (OR) values. ***Results:*** The virological response in TDF-treated CHB patients was notably superior to that of the ETV-treated CHB patients after 12-weeks [OR=1.12, 95% confidence interval (CI): 0.89–1.41], 24-weeks (OR=1.33, 95% CI: 1.11–1.61), 48-weeks (OR=1.62, 95% CI: 1.16–2.25), 72-weeks (OR=1.43, 95% CI: 0.78–2.62), and 96-weeks (OR=1.56, 95% CI: 0.87–2.81) treatment. No significant difference was observed for the virological responses in CHB patients after 48-weeks treatment with TAF or TDF. The virological response in TDF+ETV-treated CHB patients was superior to that of TDF-treated CHB patients after 24-weeks, 48-weeks (OR=1.54, 95% CI: 1.17–2.02), 96-weeks, and 144-weeks. ***Conclusions:*** The virological response in TDF-treated CHB patients was superior to that in ETV-treated CHB patients, but there was no significant difference between TAF and TDF. In addition, the therapeutic effect of TDF+ETV was superior to TDF alone.

Introduction

Hepatitis B virus (HBV) infection is a serious global health problem and patients are considered to be at high risk of developing hepatic cirrhosis and hepatocellular carcinoma (referred to herein as HCC).[1] A report from the World Health Organization indicated that 292 million individuals are positive for the hepatitis B surface antigen across the globe, and the distribution of chronic hepatitis B (CHB) patients is region-dependent.[2,3] HBV infection has become one of the principal causes of liver-related mortality globally, and approximately 700,000 HBV-related deaths occurred in 2013 alone.[3]

Tenofovir alafenamide fumarate (TAF), tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are recommended as the first-line oral drugs for patients with CHB.[4,5] Furthermore, these drugs exert good effect on the suppression of HBV replication, provide histologic improvement, and reduce the incidence of HCC after the long-term nucleos(t)ide analogue therapy.[6,7] TAF is a bioavailable prodrug of tenofovir (TFV), which is regarded as an effective therapeutic drug for both HBV and human immunodeficiency virus (*i.e.* HIV-1) infection.[8,9] A previous study found that TAF possesses greater plasma stability, safety and toleration than TDF.[10] According to the clinical trials, TAF was more likely to be safe compared to TDF, most notably for patients with bone and renal dysfunction.[11,12] Ridruejo *et al*.[13] reported that ETV had long-term effectiveness and safety for HBV patients, while some other studies have demonstrated that the rate of HBV DNA suppression achieved was less than that with TDF or TAF within 3 years.

In consideration of the inconsistency of the therapeutic effects of TAF, TDF, and ETV for patients with CHB, and whether the combination of TAF and ETV possesses a better

*Correspondence to: Yongning Xin, Department of Infectious Disease, Qingdao Municipal Hospital, 1 Jiaozhou Road, Qingdao, Shandong 266011, China. ORCID: https://orcid.org/0000-0002-3692-7655. Tel: +86-532-8278-9463, Fax: +86-532-8596-8434, E-mail: xinyongning@163.com; Shiying Xuan, Department of Infectious Disease, Qingdao Municipal Hospital, 1 Jiaozhou Road, Qingdao, Shandong 266011, China. ORCID: https://orcid.org/0000-0002-9849-1877. Tel: +86-532-8890-5508, Fax: +86-532-8890-5293, E-mail: xuansydxy@163.com

effect than single-agent TAF treatment in CHB patients, this study was designed to explore the difference of virological response with TAF, TDF, and ETV, and the combination of TAF and ETV in the patients with CHB.

Methods

Study selection

A literature search was performed in the PubMed, Cochrane Library, and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (commonly known as PRISMA) process. Studies published up to July 21, 2020 and in the English language were considered. Various combinations of the following keywords were applied in the search strategy: tenofovir alafenamide, TAF, emlidy, ETV, entecavir, ECV, Enti, En, Viread, tenofovir disoprox, TDF.

Inclusion and exclusion criteria

The inclusive criteria were as follows: 1) research type: randomized controlled trial (RCT) and observational study; 2) research subjects: patients with chronic hepatitis B and only those patients diagnosed by HBV DNA test; 3) data on virological response, defined as undetectable HBV DNA level in serum and the lower limit for undetectable HBV DNA having been determined; and 4) receipt of treatment with TDF, TAF, or ENT or combination of these drugs. The exclusion criteria were as follows: 1) research type: review; 2) data unable to be extracted or utilized; 3) data based upon animal experiments; or 4) patients co-infected with HIV or other hepato-tropic viruses.

Data extraction and quality assessment

Information including the first author, publication date, country, sample size, study type, intervention mode, and undetectable HBV DNA level were extracted from each study. The virological response rate of the intervention group and control group were pooled for the meta-analysis. The article list and extracted data were checked by a third researcher, to ensure no patient overlap was present among the different included studies. Quality of the included studies was assessed independently by two authors (Xuefeng Ma and Shousheng Liu). Any discrepancies were resolved through consensus decision upon discussion with a third author. The cohort studies were evaluated according to the Newcastle-Ottawa scale (commonly known as the NOS).[14] The NOS is comprised of the following three sections: selection (up to 4 points); comparability (up to 2 points); and, outcome (up to 3 points). The maximum score is 9 points. Study quality was classified as poor (score, 0–3), fair (score, 4–6), or good (score, 7–9). For RCTs, the updated Cochrane tool (https://www.riskofbias.info/) was used to assess the risk of bias. The updated Cochrane tool was made up of the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting bias; and other sources of bias. The high, low, or unclear risks of bias of each study were determined in those domains.

Statistical analysis

STATA 14 software (Stata Corporation, College Station, TX,
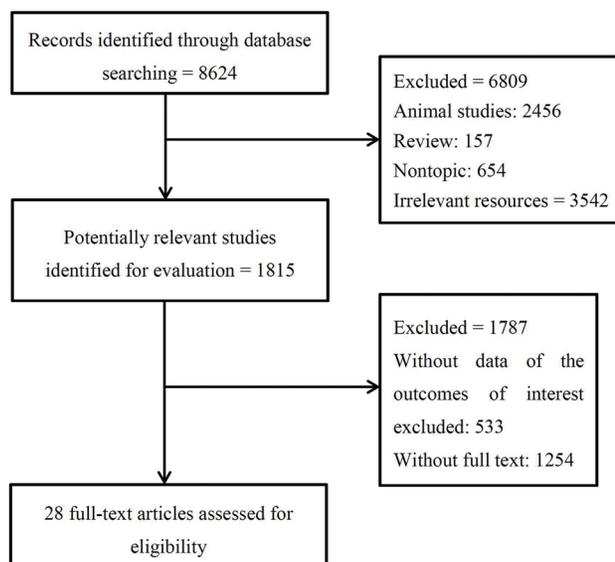
Fig. 1. Flow chart of the literature search process.

USA) was used for data analysis in this study. Dichotomous variables were expressed as odds ratio (OR; as an effective indicator) and the estimated value and 95% confidence interval (CI) were included as effect analysis statistics. For the Q statistic, heterogeneity was considered present when p was <0.1 or I^2 was >50%. A fixed-effect model was used when literature heterogeneity did not exist; otherwise, a random-effect model was used. Publication bias was calculated visually with funnel plots. Publication bias was considered significant when p was <0.05 in Begg's test. Subgroup analyses were performed according to undetectable HBV DNA level and design of the study.

Results

Literature search results and study characteristics

A total of 8,624 studies were identified as potentially relevant studies from the databases. After removing animal studies, reviews, non-topical studies and irrelevant resources, 1,815 studies were retrieved for further evaluation. After excluding studies which did not provide detailed information of virologic response and those without full-text, 28 studies were included for this meta-analysis (Fig. 1). Among these selected studies, 17 focused on the comparison of TDF vs. ETV, 5 focused on the comparison of TAF vs. TDF, and 6 focused on the comparison of TDF+ETV vs. TDF. Among these selected studies, 13 were RCTs,[15–27] 14 were cohort studies,[28–41] and only 1 was a cross-sectional study[42] (Table 1). Quality assessment suggested that all the cohort studies and RCTs possessed high quality (Table 1 and Fig. 2). Other characteristics of included studies are presented in Supplementary Table 1.

### Comparison of the virological response in TDF-treated vs. ETV-treated CHB patients

A total of 17 studies investigated the difference of virological response in patients with CHB after treatment with TDF and ETV[19,22,26–34,36–39,41,42] (Table 1). Among these studies,

Table 1. Characteristics of studies that met our inclusion criteria

	Author	Year	Country	Sample size	Study type	Follow-up in weeks	Intervention	Undetectable HBV DNA level	Study quality
	Batirel et al.[28]	2014	Turkey	195	Retrospective study	48	Received TDF (245 mg/day) or ETV (0.5 mg/day)	20 IU/mL	Good
	Cai et al.[19]	2019	China	315	RCT	144	All the drugs, either TDF capsule or ETV capsule, were provided by Cosunter Pharmaceutical (Ningde, Fujian, China)	20 IU/mL	NA
	Centeno et al.[34]	2016	Spain	64	Retrospective study	48	Initiated treatment with TDF or ETV between January 1998 and 2013	20 IU/mL	Good
	Ceylan et al.[29]	2013	Turkey	117	Retrospective study	96	Treatment with TDF or ETV	20 IU/mL	Good
	Ha et al.[30]	2016	USA	556	Retrospective study	96	Either ETV 0.5 mg daily or TDF 300 mg daily	40 IU/mL	Good
	Jayakumar et al.[31]	2012	India	39	Prospective study	24	Treated with lamivudine (100 mg/day) plus adefovir (10 mg/day) combination ETV monotherapy (0.5 mg/day) and tenofovir monotherapy (300 mg/day)	400 copies/mL	Good
	Kayaaslan et al.[32]	2017	Turkey	252	Retrospective study	96	Therapy with ETV 0.5–1 mg/day or TDF 245 mg/day	20 IU/mL	Good
	Koike et al.[22]	2017	Japan	166	RCT	24	TDF 300 mg QD and ETV 0.5 mg QD	NA	NA
TDF vs. ENT	Kwon et al.[33]	2015	Korea	79	Retrospective study	48	Treatment with TDF or ETV	20 IU/mL	Good
	Ozaras et al.[36]	2014	Turkey	251	Cohort study	72	Treatment with TDF or ETV	2*10^6 IU/mL	Good
	Park et al.[37]	2017	Korea	210	Cohort study	48	Treatment with TDF or ETV	20 IU/mL	Good
	Riveiro-Barciela et al.[38]	2017	Spain	611	Cohort study	60	ETV at dose of 0.5 or 1 mg per day, and TDF at dose of 245 mg per day	69 IU/mL	Good
	Pereira et al.[42]	2016	Brazil	294	Cross-sectional study	48	Treatment with TDF or ETV	NA	NA
	Shi et al.[39]	2016	China	96	Retrospective study	96	Treated orally with ETV at 0.5 mg/day (ETV group) and tenofovir at 300 mg/day (TDF group)	100 IU/mL	Good
	Sriprayoon et al.[26]	2016	Thailand	400	RCT	144	Receive either ETV 0.5 mg or TDF 300 mg daily	20 IU/mL	NA
	Yim et al.[27]	2018	Korea	40	RCT	48	One group received 300 mg of TDF once daily and the other received 0.5 mg of ETV once daily	120 copies/mL	NA
	Yu et al.[41]	2014	Korea	107	Retrospective study	48	Treated with TDF 300 mg daily, and the ETV group treated with ETV 0.5 mg daily	50 IU/mL	Good

Table 1. *(continued)*

	Author	Year	Country	Sample size	Study type	Follow-up in weeks	Intervention	Undetectable HBV DNA level	Study quality
	Agarwal et al.[15]	2018	United Kingdom	1,298	RCT	48	Receive 25 mg TAF or 300 mg TDF	29 IU/mL	NA
	Buti et al.[16]	2016	Spain	425	RCT	96	Receive once-daily oral doses of TAF 25 mg or TDF 300 mg, each with matching placebo	29 IU/mL	NA
	Buti et al.[17]	2017	Spain	1,298	RCT	48	Receive oral tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg TAF (elvitegravir/cobicistat/ emtricitabine/TAF) or 300 mg TDF (elvitegravir/cobicistat/ emtricitabine /TDF)	29 IU/mL	NA
TAF vs. TDF	Byrne et al.[18]	2018	Spain	1,298	RCT	96	Different doses of TAF (8, 25, 40 or 120 mg) or to TDF 300 mg	29 IU/mL	NA
	Chan et al.[20]	2016	China	873	RCT	96	Received TAF 25 mg orally once daily or TDF 300 mg orally once daily.	29 IU/mL	NA
	Jeon et al.[21]	2017	Korea	54	RCT	96	Related with TDF monotherapy (*n*=12), TDF+LAM (*n*=19), or TDF+ETV (*n*=42)	12 IU/mL	NA
	Lim et al.[23]	2015	Korea	90	RCT	48	Receive TDF (300 mg/ day) monotherapy or TDF and ETV (1 mg/day) combination therapy	15 IU/mL and 60 IU/mL	NA
	Lim et al.[24]	2017	Korea	192	RCT	144	After completing 48 weeks of randomized, parallel comparisons of TDF monotherapy (300 mg once daily) vs. TDF/ETV combination therapy, patients were eligible to continue TDF monotherapy (TDF-TDF group) or switch to TDF monotherapy (TDF/ETV-TDF group)	15 IU/mL and 60 IU/mL	NA
TDF+ETV vs. TDF	Lok et al.[25]	2012	Turkey	379	RCT	96	Receive ETV 0.5 mg plus TDF 300mg once daily or ETV 0.5 mg once daily for 100 weeks	50 IU/mL	NA
	Lu et al.[35]	2014	USA	68	Retrospective cohort study	68	At least 12 months of ETV, and were switched to TDF monotherapy (*n*=25) or ETV+TDF (*n*=43)	60 IU/mL	Good
	Wang et al.[40]	2019	China	143	Retrospective study	143	CHB patients with PVR to ETV were switched to TDF monotherapy or TDF+ETV combination therapy	100IU/mL	Good
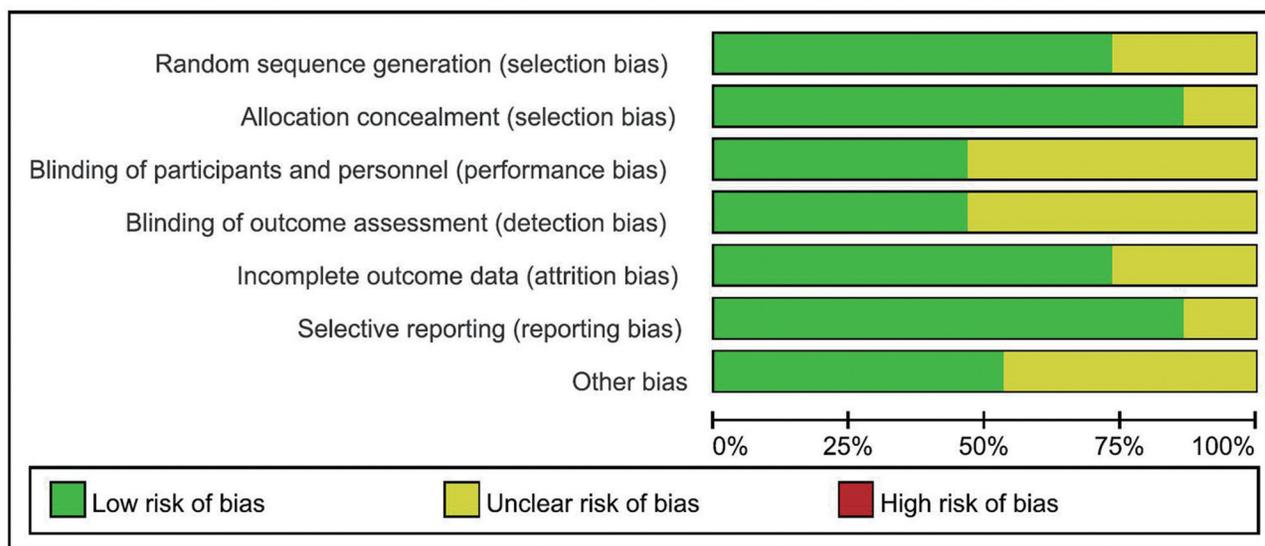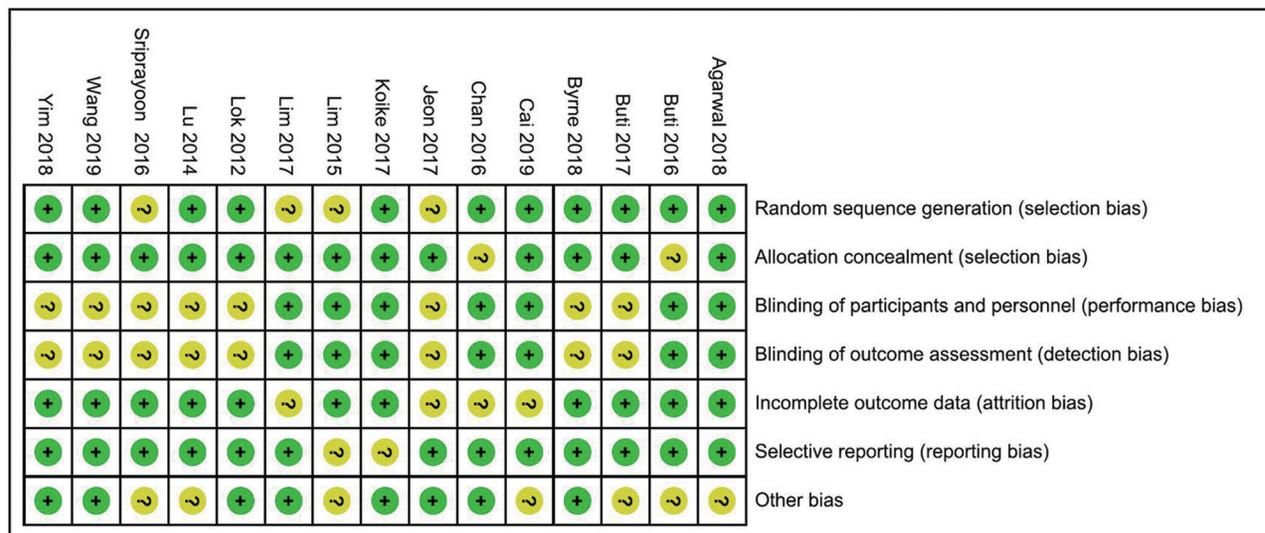
Fig. 2. Risk-of-bias summary for the included randomized controlled trials (RCTs). (A) Overall risk of bias of the included RCTs. (B) Performance of bias in each study. RCT, randomized controlled trial.

four were conducted in South Korea, four in Turkey, two in China, one in Japan, one in India, one in Brazil, one in Thailand, and one in the USA. Furthermore, 13 were observational studies, which included 12 cohort studies and 1 cross-sectional study, and 4 were RCTs. A total of 3,792 patients were involved in the 17 total studies.

Nine studies reported the virological response of patients with CHB after 12 weeks of treatment with TDF and ETV. The pooled effects of TDF and ETV on virological response were analyzed by using the fixed-effects model (p=0.547, I^2=0.0%). The results showed that the virological response of TDF was superior to that of ETV (OR=1.12, 95% CI: 0.89–1.41), but the difference was not statistically significant (p>0.05) (Fig. 3A). Thirteen studies reported the virological response of patients with CHB after 24 weeks of treatment with TDF and ETV. The outcome was demonstrated by a fixed fixed-effects model (p=0.053, I^2=42.3%),

and the pooled OR was 1.33 (95% CI: 1.11–1.61, p<0.05) (Fig. 3B). Three studies reported the virological response of patients with CHB after 36 weeks of treatment with TDF and ETV. The outcome was demonstrated by the random-effects model (p=0.128, I^2=51.4%), and the pooled OR was 0.93 (95% CI: 0.46–1.87, p>0.05) (Fig. 3C). Twelve studies reported the virological response of patients with CHB after 48 weeks of treatment with TDF and ETV. The outcome was demonstrated by the random-effects model (p=0.007, I^2=51.8%), and the pooled OR was 1.62 (95% CI: 1.16–2.25, p<0.05) (Fig. 3D). Six studies reported the virological response of patients with CHB after 72 weeks of treatment with TDF and ETV. The outcome was demonstrated by the random-effects model (p=0.001, I^2=75.1%), and the pooled OR was 1.43 (95% CI: 0.78–2.62, p>0.05) (Fig. 3E). Six studies reported the virological response of patients with CHB after 96 weeks of treatment with TDF and
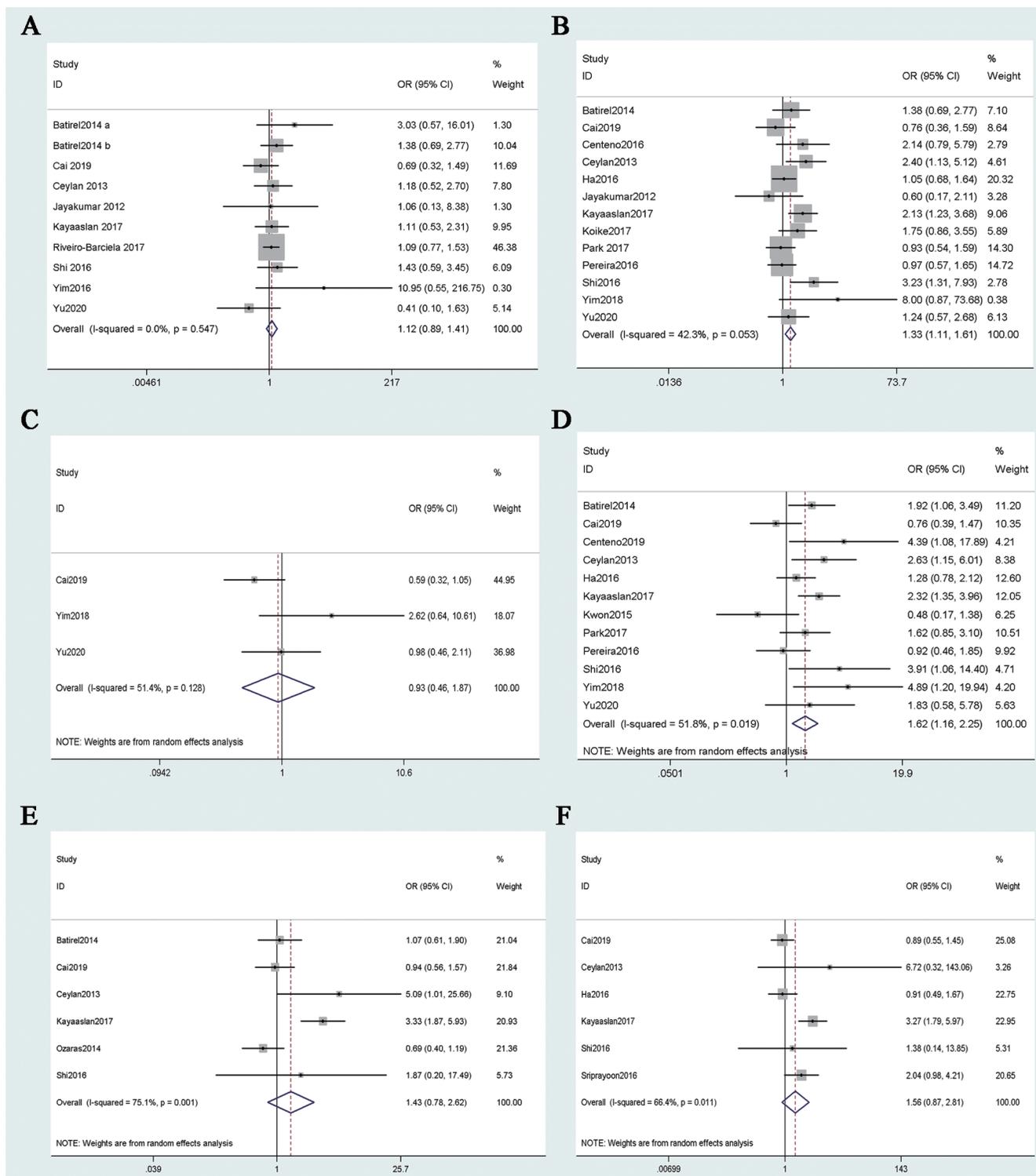
Fig. 3. Pooled odds ratios (ORs) of virological response in tenofovir disoproxil fumarate (TDF)-treated vs. entecavir (ETV)-treated chronic hepatitis B (CHB) patients. After (A) 12 weeks, (B) 24 weeks, (C) 36 weeks, (D) 48 weeks, (E) 72 weeks and (F) 96 weeks of treatment. CHB, chronic hepatitis B; ETV, entecavir; OR, odds ratio; TDF, tenofovir disoproxil fumarate.

ETV. The outcome was demonstrated by the random-effects model ($p<0.001$, $I^2=88.0\%$), and the pooled OR was 1.56 (95% CI: 0.87–2.81, $p>0.05$) (Fig. 3F). The virological response of patients with CHB after 120 weeks of treatment

with TDF and ETV was reported in one study and after 144 weeks treatment was reported in two studies; the results suggested that there was no strong difference in the virological response after treatment with TDF or ETV.
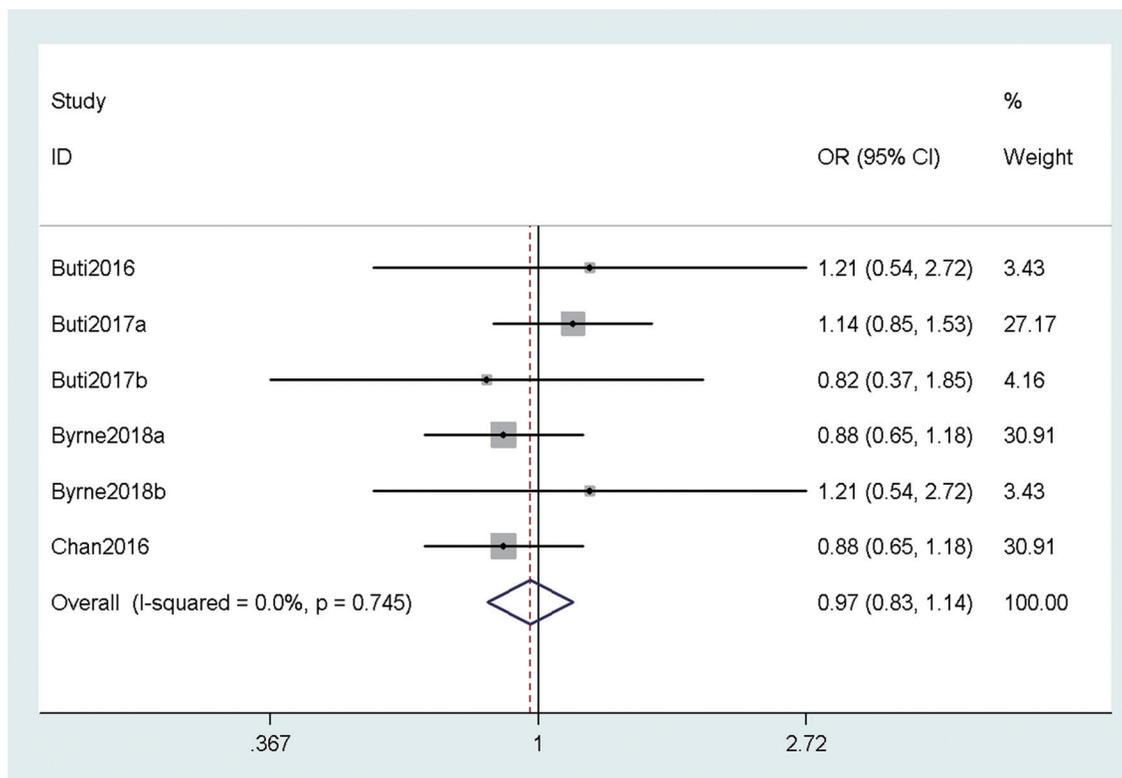
Fig. 4. Pooled OR of virological response in tenofovir alafenamide fumarate (TAF)-treated vs. TDF-treated CHB patients after 48 weeks of treatment.
CHB, chronic hepatitis B; OR, odds ratio; TAF, Tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

Comparison of the virological response in TAF-treated vs. TDF-treated CHB patients

Five of the studies investigated the difference of virological response in patients with CHB after treatment with TAF and TDF[15–18,20] (Table 1). Among those studies, three were conducted in Spain, one was conducted in the UK and 1 was conducted in China. All were RCTs, and a total of 5,192 patients were included in these studies.

Four studies reported the virological response of patients with CHB after 48 weeks of treatment with TAF and TDF. The pooled effects of TAF and TDF on the virological response were analyzed by using the fixed-effects model (p=0.783, I^2=0.0%). The results showed that the virological response of TAF was equivalent to that of TDF (OR=0.97, 95% CI: 0.83–1.14, p>0.05) (Fig. 4). The virological response of patients with CHB after 96 weeks of treatment with TAF and TDF was reported in two studies, the results suggested that there was no obvious differences in the virological response after treatment with TAF and TDF.

Comparison of the virological response in TDF+ETV-treated vs. TDF-treated CHB patients

Six studies investigated the difference of virological response in patients with CHB after treatment with TDF+ETV and TDF[21,23–25,35,40] (Table 1). Among these, four were conducted in South Korea, one was conducted in China and one was conducted in the USA. Furthermore, two studies were cohort studies and one was an RCT; a total of 926 patients were included in these studies.

The virological response of patients with CHB after 24 weeks of treatment with TDF+ETV or TDF alone was reported in two studies. The results suggested that the therapeutic effect of TDF+ETV was significantly superior to that of TDF alone. Six studies reported the virological response of patients with CHB after 48 weeks of treatment with TDF+ETV or TDF alone. The outcome was demonstrated by the random-effects model (p=0.529, I^2=0.0%), and the pooled OR was 1.54 (95% CI: 1.17–2.02, p<0.05) (Fig. 5). The virological response of patients with CHB after 96 weeks and 144 weeks of treatment with TDF+ETV or TDF alone was reported in two studies and one study, respectively. The results suggested that the therapeutic effect of TDF+ETV was significantly superior to that of TDF alone.

Discussion

In this study, we systematically compared the therapeutic effect of TDF, TAF, ETV, and TDF+ETV on CHB patients. Our results suggest that in the TDF-treated CHB patients, the virological response was markedly superior to that of ETV-treated CHB patients after 12-, 24-, 48-, 72-, and 96-weeks treatment, which supports that TDF can be superior to ETV for the treatment of CHB patients. When compared to the therapeutic effect of TAF and TDF, no obvious difference was observed, which suggests that TAF is comparable to TDF for the treatment of CHB patients. In addition, we found that the virological response in TDF+ETV-treated CHB patients was superior to that of TDF-treated CHB patients after 24-, 48-, 96-, and 144-weeks treatment, which suggests that TDF combined with ETV exerts a better therapeutic effect for CHB patients than TDF alone.

TDF and ETV are two types of nucleos(t)ide analogues that can efficiently inhibit the replication of HBV via the
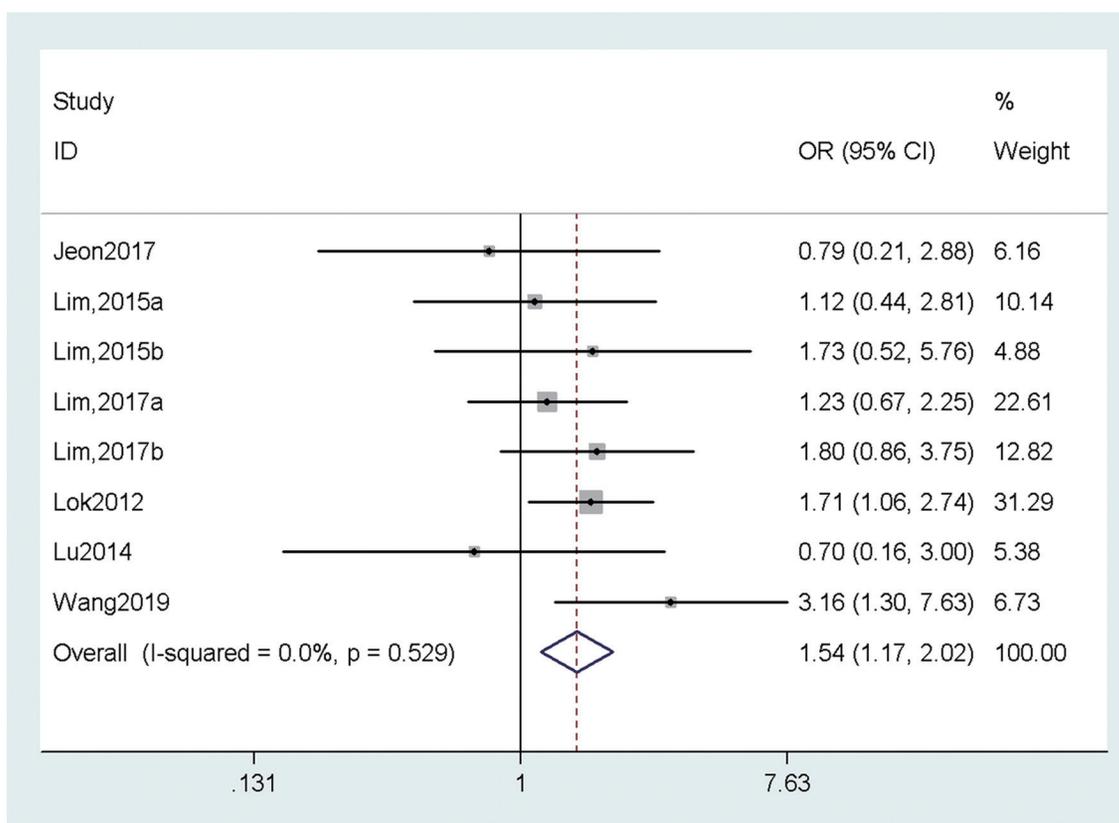
Fig. 5. Pooled OR of virological response in TDF+ETV-treated vs. TDF-treated CHB patients after 48 weeks of treatment. CHB, chronic hepatitis B; ETV, entecavir; OR, odds ratio; TDF, tenofovir disoproxil fumarate.

blockade of DNA polymerase and reverse transcriptase, respectively.[43] Nowadays, TDF and ETV are widely used for patients with CHB, due to their potent antiviral activities. The therapeutic effect of TDF and ETV in CHB patients has been investigated in some studies, but the conclusions have not been consistent. Yim *et al*.[27] conducted a RCT to investigate the virological response in CHB patients upon treatment with TDF or ETV. They found that when patients were switched to TDF from ETV, the HBV DNA level was significantly lower than that detected in the ETV treatment group.

In this meta-analysis, we summarized all the relative studies to compare the value of TDF and ETV on the treatment of CHB. We found that TDF was superior to ETV for the treatment of CHB patients. However, there were some inconsistencies observed regarding safety. Cai *et al*.[19] reported that both TDF and ETV were generally well tolerated, and the common adverse events were similar with no obvious fluctuation of the estimated glomerular filtration rate (commonly known as eGFR) found during the observational period between the TDF group and ETV group. Meanwhile, Centeno *et al*.[34] reported that after 48 weeks of treatment, 19.4% of patients in the TDF group showed eGFR <60 mL/min/1.73m^2 vs. 15.6% in the ETV group, which demonstrated the better effect achieved with TDF than ETV.

TAF is a newly developed prodrug of TFV, which can facilitate better entry of TFV into hepatocytes than TDF. Agarwal *et al*.[15] reported that after treatment with TAF, patients possessed higher intracellular concentrations of TFV and lower plasma concentrations of TFV compared to those who were on treatment with TDF. Our meta-analysis indicated that there was no significant difference in the virological responses of patients treated with TAF vs. TDF. Regarding

safety, Chan *et al*.[7,20] found that the unique pharmacokinetic profile of TAF had caused the declined rates of TFV-related major adverse events, kidney dysfunction, and bone mineralization, when compared with TDF. Furthermore, many studies have displayed that the levels of low-density lipoprotein, fasting total cholesterol, and high-density lipoprotein were all reduced in patients with HIV co-infection;[44,45] although, the precise mechanism for these changes remains unclear. Besides the TAF vs. TDF comparison results, we also found the TDF+ETV combination can bring about an effective virological response compared to TDF alone in CHB patients. Whereas, Wang *et al*.[40] found slightly increased serum creatinine level and decreased serum phosphorus level in TDF+ETV-treated CHB patients, but with both of which being within the normal range.

The therapeutic effect of TDF or ETV in CHB patients may be influenced by the genotype of HBV. Lok *et al*.[25] demonstrated that loss of hepatitis B surface antigen and hepatitis B e antigen seroconversion signifies that patients with HBV genotype C infection enjoyed better performance of TDF+ETV combination than ETV alone; however, the performance of TDF+ETV combination was poorer than ETV alone for HBV genotypes A, B and D. In addition, the main indication and characteristics of patients treated by TDF+ETV combination was drug resistance. Except for patients in the study by Lok *et al*.,[26] most of the patients in the studies using TDF+ETV combination have been reported to have resistance to ETV, lamivudine or adefovir dipivoxil.[25]

There are several inherent limitations to this study, which must be considered. First, only two studies were included to compare the therapeutic effect of TDF+ENT vs. TDF alone; therefore, more RCTs are needed to supported our conclu-

sions. Second, almost all of the included studies were RCTs or interventional cohort studies, and a potential source of bias might have been introduced. Third, age, sex, hepatitis B e antigen status, cirrhosis stage, and HBV DNA level before therapy, duration of previous therapy, and baseline HBV DNA level may be factors associated with virologic response but which were not taken into account in our meta-analysis.

Conclusions

In summary, the therapeutic effect of TDF, ETV, TAF, and TDF+ETV in patients with CHB was investigated in this study. The virological response in TDF-treated CHB patients was superior to that achieved in the ETV-treated CHB patients, but no significant difference of virological response was found between TAF-treated and TDF-treated CHB patients. In addition, the therapeutic effect of TDF+ETV was superior to that of TDF. These conclusions were made from the available studies published to recent time, and more clinical RCTs or observational studies should be conducted to verify them. Also, the drug safety of TAF, TDF, and TDF+ETV should be investigated more systematically.

NA, not available or not applicable. CHB, chronic hepatitis B; ETV, entecavir; TAF, Tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Acquisition of data, analysis and interpretation of data, drafting and final approval of the article (XM, SL); acquisition, analysis and interpretation of data (MW, YW, SD); study design and revision of the article (YX, SX). All authors have read and approved the manuscript.

Data sharing statement

No additional data are available.

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