Int J Clin Exp Med 2015;8(11):20111-20122
www.ijcem.com /ISSN:1940-5901/IJCEM0013659

Original Article

Comparison of the efficacy of tenofovir monotherapy versus tenofovir-based combination therapy in adefovir-experienced chronic hepatitis B patients: a systematic review and meta-analysis

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Received July 29, 2015; Accepted November 4, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Background: Chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide. Tenofovir monotherapy or tenofovir-based combination therapy have achieved promising results in the treatment of chronic hepatitis B patients who failed adefovir therapy. Objective: The goal of this study was to assess the efficacy of tenofovir monotherapy compared with tenofovir-based combination therapy for treatment of adefovir-experienced chronic hepatitis B (CHB) patients. Methods: randomized and non-randomized control trials directly comparing tenofovir monotherapy and tenofovir-based combination therapy were searched in PUBMED, MEDLINE, EMBASE database up to April 30, 2015. The data were analyzed with Review Manager (v.5.3). Results: Seven articles (total of 478 patients) met entry criteria. The results found that the rates of undetectable hepatitis B virus DNA levels (64.7% vs. 68.5%, P = 0.58 for 24 weeks; 71.4% vs. 71.7%, P = 0.76 for 48 weeks; 71.6% vs. 73.0%, P = 0.92 for 96 weeks), alanine aminotransferase (ALT) normalization (72.6% vs. 69.2%, P = 0.46 for 48 weeks; 72.8% vs. 75.0%, P = 0.74 for 96 weeks) and hepatitis Be antigen loss (5.0% vs. 0, P = 0.43 for 48 weeks; 16.5% vs. 12.5%, P = 0.43 for 96 weeks) were not significantly different between the TDF alone and the TDF-based group. Moreover, the rate of adverse reactions was also not significantly different between the 2 groups (P = 0.06 for 96 weeks). Conclusions: TDF monotherapy and TDF-based combination therapy are similarly effective and safe in adefovir-experienced CHB patients after 48 weeks and 96 weeks of antiviral therapy. Nevertheless, large scale randomized control trials should be carried out to elucidate the long-term outcome of TDF treatment.

Keywords: Chronic hepatitis B, tenofovir monotherapy, tenofovir-based combination therapy, adefovir failure, adefovir-resistant

Introduction

Chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide, especially in Asia [1-3]. Nowadays, treatment of chronic hepatitis B (CHB) has greatly improved with the availability of nucleos(t)ide analogs (NAs) [4-6]. The sustained suppression of serum HBV DNA to very low or undetectable levels by NAs has been shown to be associated with the prevention of progression of liver disease and inhibition of the development of hepatocellular carcinoma [7-9]. Unfortunately, as the duration of NAs treatment is prolonged, the risk of development of drug resistance increases with lesser potent and lower genetic barrier drugs such as lamivudine (LAM) and adefovir (ADV) [7, 10, 13], which can lead to a rebound in HBV DNA, progressive liver injury, and increased disease complications [11, 12].

ADV was approved in 2002 as an HBV therapy and is effective in the setting of LAM-resistance [14]. However, long-term use of ADV leads to the development of resistant HBV mutants and viral breakthrough [15]. When ADV was used in patients who failed with LAM therapy, the rate of genotypic resistance to ADV reached 25% at

24 months [16]. The treatment options for patients who fail LAM and ADV monotherapy have been limited. Current treatment guidelines suggest a rescue therapy based on a switch to a more potent drug, or the combination of 2 drugs with complementary cross-resistance profiles [17].

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue closely related to ADV, has similar antiviral activity against wild type and LAM-resistant HBV as ADV in *in vitro* studies [18]. Clinical studies have observed that TDF is more effective in suppressing HBV replication than ADV [19, 20]. In treatment-naive patients, TDF was shown to durably suppress HBV replication and no drug resistant mutant has been detected with up to 5 years of continuous therapy [21-23]. TDF has also been shown to be highly efficacious in patients with amivudine-resistant HBV infection and even in patients who failed ADV therapy [24-27]. However, clinical studies evaluating the use of TDF in ADV-experienced populations have produced varied results. Several controlled studies have demonstrated that TDF monotherapy and tenofovir-based combination therapy had similar effective in maintaining long-term viral suppression in ADV-experienced patients, with virologic response independent of baseline ADV resistant mutation [29, 31, 34]. However, some other studies showed that the persistent or emerging ADV resistant mutation reduced antiviral response during TDF monotherapy, and suggested that combination treatment might be more effective in ADV resistant cases [25, 32, 33]. Nonetheless, due to the small sample sizes of these studies and subsequent limited data for comparing TDF monotherapy with tenofovir-based combination therapy, the efficacy of TDF monotherapy is still controversial for patients who harbour HBV mutants resistant to ADV. Moreover, it remains unclear whether tenofovir-based combination therapy provides better outcomes than TDF monotherapy for the treatment of these patients.

Herein, we conducted this systematic review and meta-analysis by integrating published TDF-based data to compare the efficacy of TDF monotherapy versus tenofovir-based combination therapy in the treatment of adefovir-experienced chronic hepatitis B patients and ultimately provide evidence for clinical options.

Materials and methods

Search strategy

We searched PUBMED, MEDLINE, EMBASE, CNKI (China National Knowledge Infrastructure), the VIP database, the Wanfang database up to March 30, 2015. The following keywords were used for the search: hepatitis B, tenofovir, adefovir-resistant and adefovir refractory (and multiple synonyms for each term) were used to find relevant citations. In addition, reference lists from retrieved documents were reviewed, and a manual search was conducted to supplement the computer search. The search results were downloaded to a reference database and were further screened by 2 authors (Wang HL and Yang XD). No protocol exists for this systematic review.

Inclusion and exclusion criteria

The following inclusion criteria were used for this meta-analysis:

(1) randomized and non-randomized control trials (included cohort or case-control studies), (2) study population consisting of patients, regardless of sex, age, and race, with chronic hepatitis B who were naïve to TDF, previous failure of lamivudine therapy and current treatment with adefovir dipivoxil (with or without lamivudine), and (3) intervention therapies of TDF alone versus TDF plus a nucleoside analogue. The following types of studies were excluded: (1) studies of patients with prior exposure to TDF for > 1 week, evidence of decompensated liver disease, any malignant neoplasm or coinfection with hepatitis C, hepatitis D or HIV and previous liver transplant, (2) studies not reporting any efficacy measures or not conveying sufficient statistical information, and (3) studies not including either TDF monotherapy and TDF plus a nucleoside analogue combination therapy.

Efficacy measures

Efficacy was considered for patients 24, 48 and 96 weeks post therapy by considering the following: HBV-DNA level (< 400 copies/ml), ALT normalization rate (< 40 IU/ml), HBeAg loss rate, and drug safety (adverse events, laboratory abnormalities, deaths, tolerability, etc.).

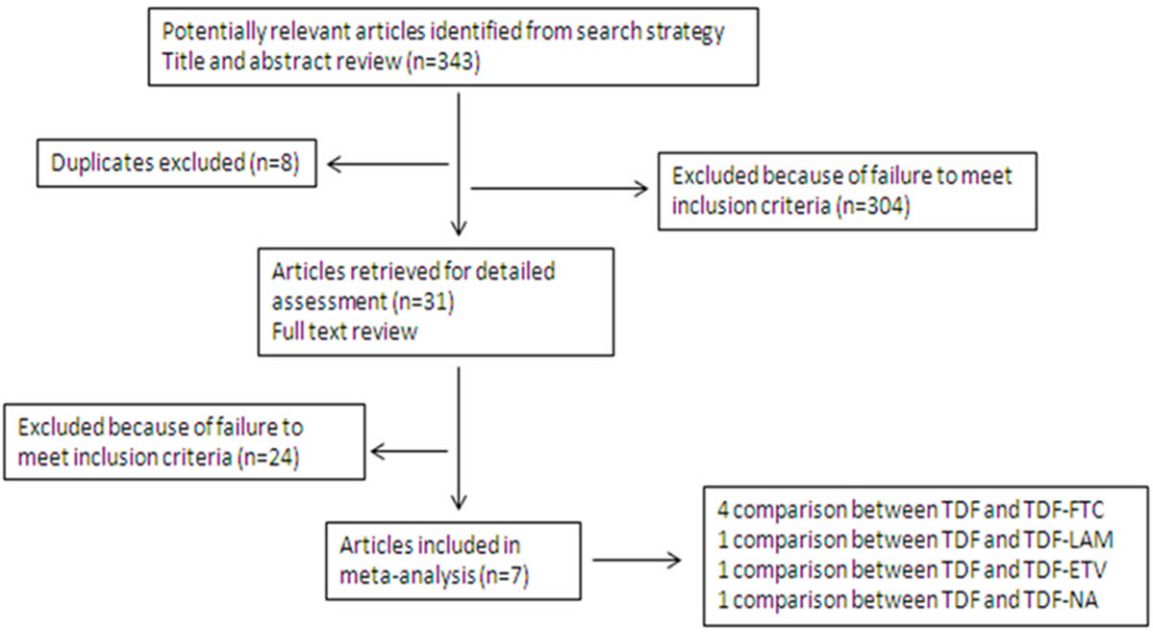

Figure 1. Flow diagram. Flow diagram of the studies identified. TDF = Tenofovirdisoproxil fumarate; FTC = emtricitabine; LAM = lamivudine; ETV = entacavir; NA = nucleoside analogue.

Data extraction

Data extraction was assessed independently by two reviewers (Wang HL and Yang XD). Discrepancies among reviewers were resolved by discussions between the reviewers or by a third person (Ning QL). Basic information obtained from each eligible trial included the study design (randomization, allocation concealment, blinding method, description of withdrawals and dropouts), patient characteristics, numbers in each group, related study results and treatment duration. Data were reviewed to eliminate duplicate reports of the same trial.

Quality assessment and statistical analysis

The risk of bias of included trials was assessed by the Cochrane Collaboration's tool. The data was conducted on continuous and dichotomous outcomes and assessed by the meta-analytical techniques. The x^2 and I^2 test were first calculated to assess the heterogeneity of the included trials. For *P* values more than 0.1, the assumption of homogeneity was valid, and the fixed-effects model was used; otherwise, data need to be dealt with the random-effects model because of the heterogeneity. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using either the fixed-effects model (M-H methods) or random-effects model (D-L methods). A two-tailed *P* value of less than 0.05 suggested statistically significant. All calculations of this meta-analysis were performed by Review Manager (v.5.3). Funnel plots from Revman (v5.3) were used to assess the risk of publication bias. Egger's and Begg's test from Stata13 were further to determine the risk of publication bias by the *P* value.

Results

Study characteristics and quality assessment

The search strategy was summarized in **Figure 1**. A total of seven studies met the inclusion criteria for this review [28-34], including 478 patients. 248 patients were treated with TDF monotherapy and 230 patients were treated with tenofovir-based combination therapy. Among tenofovir-based combination therapy, 4 studies used TDF-FTC [29-32], 1 used TDF-LAM [33], 1 used TDF-ETV [34], and 1 used TDF-NA [28]. Among the 7 studies identified, 6 studies [29-34] were published in English and 1 studies [28] were published in Korean. All seven studies [28-34] were published in full-text form. The characteristics of each study are listed in **Table 1**.

The quality assessment of included studies was performed using Cochrane Collaboration's tool with the outcome shown in **Figure 2**. The percentages of low risk of performance bias

Table 1. Characteristics of cases included in the meta analysis

Articles numbers	Region	Treatment	Study design	M/F	Mean age (yr)	Regimen		Mean HBV DNA (log10 copies/ml)	Mean ALT level (IU/L)	% HBeAg+	ADV-, LAM- or ADV- and LAM-resistance n (%)
						TDF	combination				
Choi KH (2015) N (76)	Korea	TDF vs. TDF-nucleoside analogue combination	retrospective cohort study	56/20	50	NA	NA	4.4	31	81.6	12 (15.8) ADV-R 38 (50.0) LAM-R 5 (6.6) ADV-R and LAM-R
Berg T (2014) N (105)	German	TDF VS. TDF+FTC	prospective, randomized, double-blind, double-dummy, 168-week clinical trial	NA	NA	300 mg/d	FTC:200 mg/d TDF:300 mg/d	6.0	111	NA	16 (15.2) ADV-R 14 (13.3) LAM-R 13 (12.4) ADV-R and LAM-R
Lavocat F (2013) N (17)	France	TDF VS. TDF+FTC	randomized in a double-blind trial of 48 weeks	16/1	38.6	NA	NA	5.69	113.99	70.6	10 (58.8) ADV-R 3 (17.6) LAM-R 2 (11.8) ADV-R and LAM-R
Berg T (2010) N (105)	10 in the United States, 10 in Germany, 7 in France, and 1 in Spain	TDF VS. TDF+FTC	a randomized, double-blind, double dummy, 168-week study	38/15	40	300 mg/d	FTC:200 mg/d TDF:300 mg/d	5.96	58.2	73.3	19 (18.1) ADV-R 25(23.8) LAM-R
Ten J (2008) N (13)	America	TDF VS. TDF+FTC	retrospective cohort study	NA	50.8	NA	NA	6.72	103.1	84.6	7 (53.8) ADV-R 5 (38.5) LAM-R
Patterson SJ (2010) N (60)	Australia	TDF VS. TDF+LAM	prospective open-label multicentre trial	46/60	48.5	300 mg/d	NA	5.33	49	66.7	17 (28.3) ADV-R 20 (33.3) LAM-R
Lim YS (2015) N (102)	Korea	TDF VS. TDF+ETV	a multicentre randomized open-label trial	88/14	50	300 mg/d	ETV:1 mg/d TDF:300 mg/d	3.38	32	88.2	102 (100) ADV-R

TDF = tenofovir; ADV = adefovir; LAM = lamivudine; FTC = emtricitabine; ETV = entecavir.

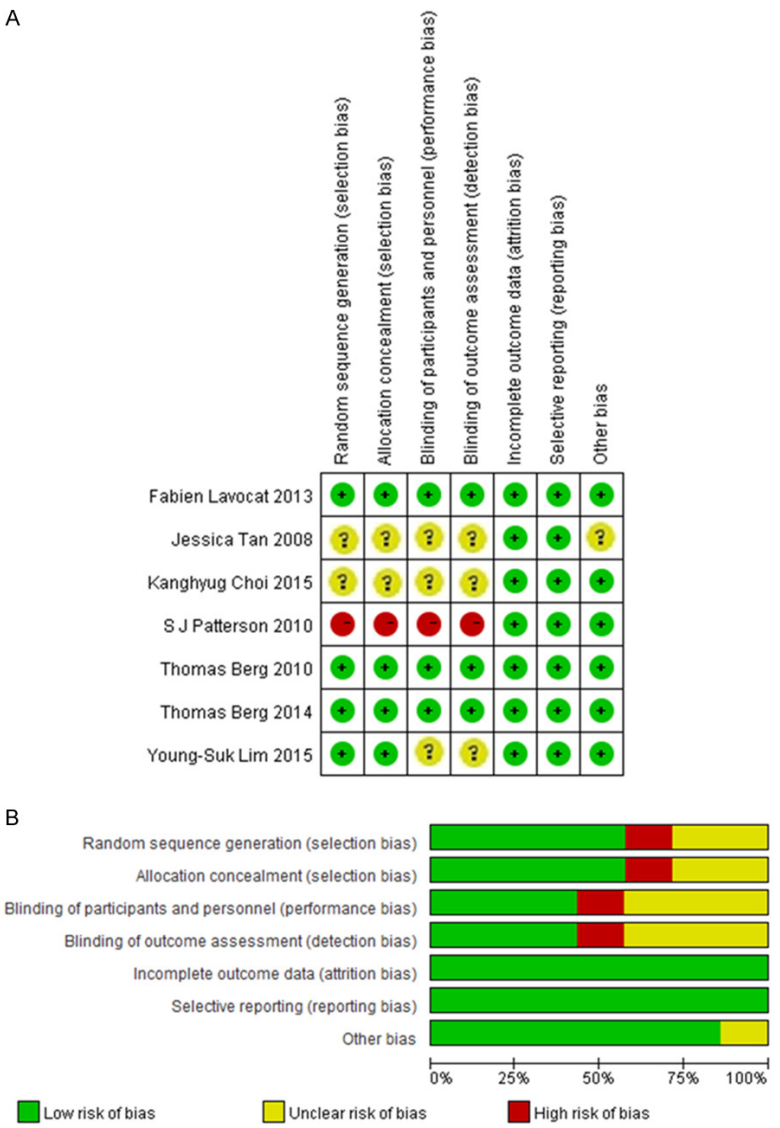

Figure 2. Assessment of risk of bias. A. Summary of risk of bias for each trail assessed, plus sign was for a judgment of Yes or low risk of bias, minus sign was for a judgment of No or high risk of bias, and question mark was for a judgment of Unclear, or uncertain risk of bias; B. Risk of bias graph about each risk of bias item presented as percentages across all included studies.

and the detection bias were less than 50% according to the description of each study. The percentages of low risk of bias of random sequence generation, allocation concealment, incomplete outcome data, selective reporting and other bias were all more than 50%. The outcome of risk of bias graph showed that there was low risk of bias in this meta-analysis.

Virological response

Three studies [29-31] reported the information of 24-week virological response contained 227 patients. At week 24 of treatment, 64.7% (75/116) of patients in the TDF group and 68.5% (76/111) of patients in tenofovir-based combination group reached undetectable HBV DNA levels. No significant heterogeneity existed across studies (P = 0.98; I^2 = 0%). In the fixed-effect model, no significant difference was determined between the two groups in rates of HBV DNA undetectability through 24 weeks of treatment (RR = 0.95, 95% CI = 0.79-1.14, P = 0.58; **Figure 3**). Seven studies [28-34] contained 478 patients reported HBV DNA levels of 48-week treatment. 71.4% (177/248) of patients in the TDF group and 71.7% (165/230) of patients in the combination group reached undetectable HBV DNA levels post 48-week of therapy. No significant heterogeneity existed across studies (P = 0.77, I^2 = 0%). In the fixed-effect model, no significant difference was determined between the two groups in rates of HBV DNA undetectability through 48 weeks of treatment (RR = 1.02, 95% CI = 0.91-1.13, P = 0.76; **Figure 3**). Three studies [29, 33, 34] contained 267 patients reported HBV DNA levels post 96 weeks of therapy. At week 96 of treatment, 71.6% (101/141) of patients in the TDF group and 73.0% (92/126) of patients in the tenofovir-based combination group reached undetectable HBV DNA levels. No significant heterogeneity existed across studies (P = 0.32, I^2 = 13%). In the fixed-effect model, no significant difference was determined between the two groups in rates of HBV DNA undetectability through 96 weeks of treatment (RR = 0.99, 95% CI = 0.86-1.14, P = 0.92; **Figure 3**).

Biochemical response

In this analysis, three studies [31, 32, 34] reported ALT levels post 48-week of therapy in

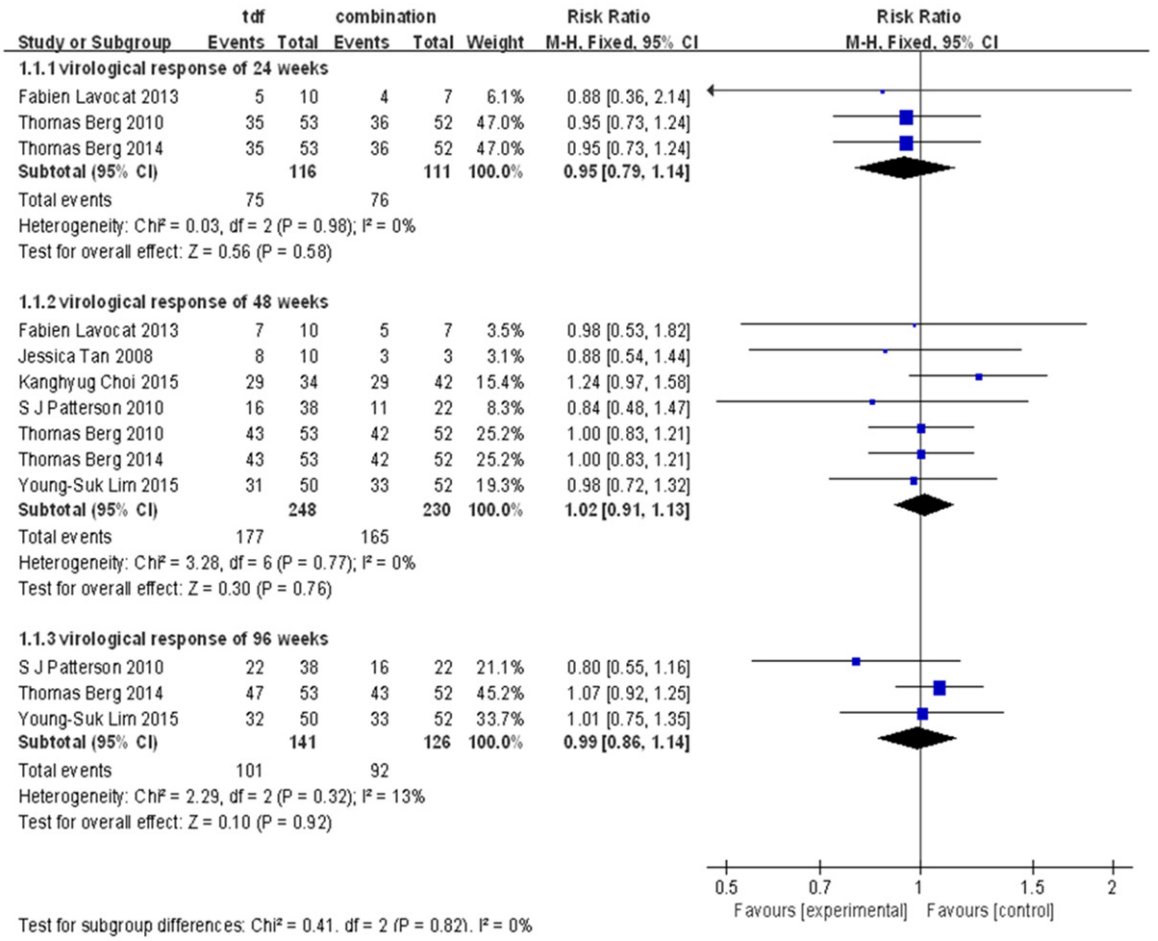

Figure 3. Virological response. Comparison of rates of undetectable HBV DNA levels between TDF monotherapy and combination therapy.

TDF group and TDF-based combination group. At the week 48 of treatment, the rates of ALT normalization were 72.6% (82/113) for TDF therapy, and 69.2% (74/107)for the combination therapy. As shown in **Figure 4A**, no heterogeneity found in the data (P = 0.30, I^2 = 16%). In fixed-effects models, no significant difference between the two groups was observed (RR = 1.07, 95% CI = 0.90-1.27, P = 0.46).

Only two studies [29, 34] reported the information of 96-week ALT levels which contained 207 patients. At the week 96 of treatment, the rates of ALT normalization were 72.8% (75/103) in the TDF group and 75.0% (78/104) in the combination group. As shown in **Figure 4A**, no heterogeneity found in the data (P = 0.83, I^2 = 0%), the meta-analysis showed that there was no significant difference between two groups in the 96 weeks (RR = 0.97, 95% CI = 0.83-1.14, P = 0.74) of the biochemical response.

Serological response

Two studies [32, 34] reported the rate of HBeAg loss post 48-week of TDF or TDF-based treatment. 5.0% (3/60) of patients in the TDF group achieved HBeAg loss, but none (0/55) of patients in the combination group achieved HBsAg loss. As shown in **Figure 4B**, no heterogeneity found in the data (P = 0.80, I^2 = 0%), the rates of HBsAg loss between two groups were no significant different at weeks 48 (RR = 2.34, 95% CI = 0.29-18.92, P = 0.43).

Two studies [29, 34] reported the information of HBeAg loss post 96-week of TDF or TDF-based treatment. 16.5% (17/103) of patients in the TDF group and 12.5% (13/104) of patients in the combination group achieved HBeAg loss at weeks 96. As shown in **Figure 4B**, no heterogeneity found in the data (P = 0.13, I^2 = 56%), and no significant difference of the rates of

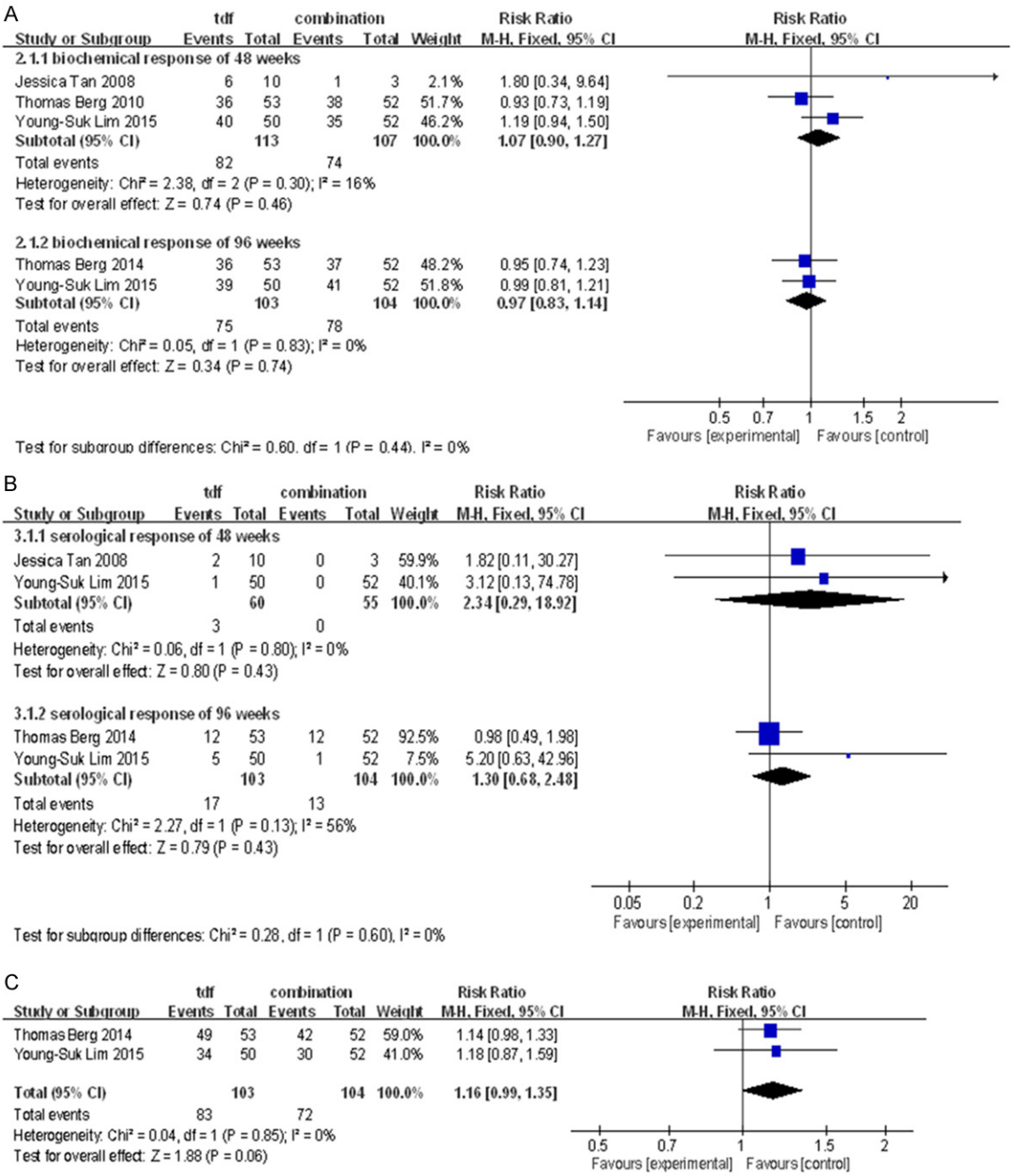

Figure 4. Biochemical response, serological response and safety. A. Comparison of serum ALT levels between TDF monotherapy and combination therapy. B. Comparison of serological response between TDF monotherapy and combination therapy. C. Comparison of safety between TDF monotherapy and combination therapy.

HBsAg loss were observed between the two groups at weeks 96 (RR = 1.30, 95% CI = 0.68-2.48, P = 0.43).

Safety

Two studies [29, 34] reported the information of safety through weeks 96 of TDF monotherapy and TDF-based combination therapy. In weeks 96 of treatment, 80.6% (83/103) of patients in the TDF group and 69.2% (72/104) of patients in the combination group had adverse reactions, and safety profiles were not significantly different between two groups (RR = 1.16, 95% CI = 0.99-1.35, P = 0.06; **Figure 4C**). Berg et al. [29] reported that both TDF and FTC/TDF were well tolerated in the treatment period. The most frequent adverse events in

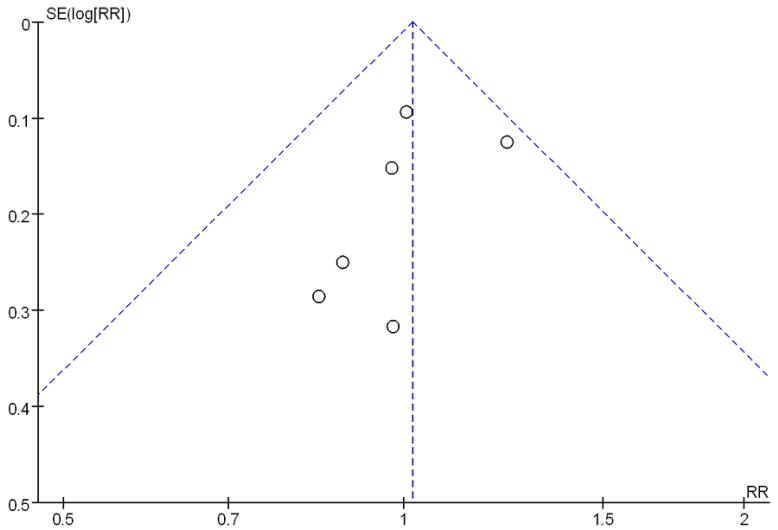

Figure 5. The funnel plot of virological response of 48 weeks.

both treatment groups were nasopharyngitis (27%), headache (24%), and fatigue (17%), and no patient experienced an on-treatment hepatic flare and renal adverse events. Lim et al. [34] reported that mean eGFR and serum phosphate levels were significantly higher compared with those at baseline (P = 0.01 and 0.04, respectively) at weeks 48 of TDF or TDF/ETV treatment, but no significant difference were observed between two groups. In addition, they found that the proportion of patients with osteoporosis and osteopenia was 8.2% (8/98) and 31.6% (31/98) respectively, at week 96, which was not significantly different between TDF and TDF/ETV groups (P = 0.61).

Publication bias

The shapes of the funnel plot for virological response showed obvious asymmetry (**Figure 5**), which were mainly because the number of studies included in this meta-analysis was small, resulting in the asymmetry of funnel plot which could not indicate the publication bias [43]. However, the Egger's test (P = 0.866) and Begg's test (P = 0.851) indicated that there is no publication bias. Therefore, according to the results from Egger's test and Begg's test, no obvious publication bias occurred in included studies.

Discussion

Incomplete virological response to ADV has been observed in patients with lamivudine-resistant hepatitis B virus (HBV) infection and may be associated with developing resistance and disease progression [35, 36]. The treatment options for patients who fail with LAM and ADV monotherapy have been limited. Sequential nucleos(t)ide monotherapy or combination treatment has been used for treatment of CHB patients with antiviral resistance. ADV was used for second line treatment of LAM resistant patient, however, ADV resistance and viral breakthrough occurred frequently [37, 38]. ADV and LAM combination therapy reduces the development of ADV resistance and has been a practical option for treatment of LAM resistance [39]. However, the antiviral efficacy of ADV and LAM combination was not satisfactory. Recent several studies have shown that TDF monotherapy or TDF plus nucleos(t)ide induced potent and long-lasting antiviral response for rescue therapy in patients with lamivudine-resistant and incomplete virological response to ADV HBV [40, 41]. Meanwhile, more promising results were shown by multiple studies claiming that both TDF monotherapy and TDF plus nucleos(t)ide are similar in both efficacy and safety in treatment of these patients [29, 31, 34]. Due to the small sample sizes of past studies and subsequent limited data for comparing the two treatments, a more definitive conclusion is lacking. Therefore, this study provided, for the first time, a meta-analysis comparing the antiviral efficacy of TDF monotherapy and TDF plus nucleos(t)ide therapy in adefovir-experienced chronic hepatitis B patients, in terms of HBV DNA undetectability, ALT levels, HBeAg Loss and adverse reactions.

Undetectable HBV DNA level is a very important indicator for the treatment of CHB. The sustained suppression of serum HBV DNA to very low or undetectable levels has been associated with the prevention liver disease progression and inhibition of the development of long-term complications [27, 42]. In this study, the proportion of patients with serum HBV-DNA levels < 400 copies/mL were 64.7%, 71.4%, 71.6% and

68.5%, 71.7%, 73.0% after 24, 48, 96 weeks of TDF monotherapy and TDF based combination therapy, respectively. Meanwhile, no significant differences in these rates were observed between TDF and combination therapies based on TDF, such as FTC plus TDF, LAM plus TDF, or ETV plus TDF (shown in **Figure 1**). Berg et al. [29] reported that TDF monotherapy and combination of TDF and emtricitabine had similar efficacy in patients with incomplete virological response after ADV therapy. The virological response was independent of pre-existing ADV or LAM resistant mutation. Tan et al. [32] reported that TDF monotherapy or combination with emtricitabine had a potent antiviral activity in patients who showed ADV resistance or suboptimal response, but the persistent or emerging ADV resistant mutation reduced the antiviral response to TDF monotherapy. Thus, they suggested that combination treatment might be more effective in ADV resistant cases. In the current study, although overall 308 of 478 (64.4%) patients were shown to harbor mutations associated with resistance to ADV and/or LAM at baseline, and they were almost equally enrolled into the two groups, the results of our meta-analysis demonstrated that TDF monotherapy was as effective as TDF-based combination therapy in maintaining long-term viral suppression in patients with a suboptimal response to adefovir. Therefore, the role of combination of nucleoside with TDF is still under investigation. A randomized controlled trial is needed to evaluate the efficacy and resistance incidence of TDF based combination therapy in LAM or ADV resistant HBV patients [32].

ALT level is a biomarker reflecting host immune response against virus-infected hepatocytes. ALT normalization usually follows a virological response and indicates cession of ongoing liver injury. In our meta-analysis, the proportion of patients with ALT normalization were 72.6%, 72.8% and 69.2%, 75% through 48, 96 weeks of TDF monotherapy and TDF based combination therapy, respectively. Moreover, the rates of ALT normalization were not significantly different between the two treatments, which indicated that both the treatment options significantly improved liver function.

HBeAg is a protein expressed by pre-C gene. HBeAg loss occurs with the rise of immunomodulatory effect which can suppress HBV DNA replication. In the present study, the rate of HBeAg loss were 5% (3/60) and 16.5% (17/103) in the TDF group, and 0 (0/55) and 12.5% (13/104) in the combination group through 48 and 96 weeks of therapies, respectively. No significant difference was observed between the two treatments.

Although oral nucleoside analogues are known to have relatively few side effects and are generally tolerated more than interferon, it is necessary to monitor long-term potential risks. In this study, 80.6% (83/103) of patients in TDF group and 69.2% (72/104) of patients in combination group had adverse reactions through weeks 96 of treatment, and no significant different was observed between two groups. The most frequent adverse events in both treatment groups were nasopharyngitis, headache, and fatigue, and no patient experienced an on-treatment hepatic flare and renal adverse events. In addition, both TDF and TDF-based combination therapy were well tolerated in the period of treatment, and no resistance to TDF was detected in any patient included in our meta-analysis.

Several limitations regarding our systematic review require comment. Firstly, some studies had a small sample size and were not RCTs, and some of the reports' experimental control was not very balanced. Secondly, it has been reported that some factors, geographic, ethnic or disease status (such as resistance profile and baseline disease characteristics) differences are possibly associated with agent efficacy. Thirdly, among tenofovir-based combination therapy, 4 studies used TDF-FTC, 1 used TDF-LAM, 1 used TDF-ETV and 1 used TDF-NA, which might affect the consistency of the results. Besides, the rates of virologic breakthrough could be not conducted because of deficiency of this information in the study.

In conclusion, our meta-analysis results demonstrated that TDF monotherapy and TDF-nucleoside analogue combination therapy are comparable in efficacy and safety to sustain long-term HBV DNA suppression with limited side effects in patients with incomplete virological response to ADV and lamivudine- and/or adefovir-associated resistance mutations. Nonetheless, more double blinding and large scale randomized control trials should be carried out to remedy above shortcomings, and to

elucidate the long-term outcome of TDF treatment.

Acknowledgements

The work was supported by grants from the National Natural Science Foundation of China (No: 30971220).

Disclosure of conflict of interest

None.

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