Comparison of renal safety of Telbivudine and Entecavir in Chronic Hepatitis B patients with renal impairment: A meta-analysis

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Research

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Abstract

Background: This study aimed to evaluate the renal safety of telbivudine (LdT) and entecavir (ETV) in chronic hepatitis B (CHB) patients with renal impairment.

Methods: Studies published from January 1, 2010 to February 1, 2020 were identified using the PubMed, Web of Science, Scopus, Cochrane Library, ClinicalTrials.gov and CNKI (China National Knowledge Infrastructure). Finally, a total of 7 studies (1088 patients) with eGFR outcomes were retrieved and analyzed. The meta-analysis was conducted using RevMan 5.3.

Results: The results of the 7 eligible studies analyzed suggested that the eGFR was both improved after LdT and ETV treatment. Compared with the baseline level, the eGFR was significantly improved with LdT ($7.02 \text{ mL/min/1.73 m}^2$) while slightly improved with ETV ($1.72 \text{ mL/min/1.73 m}^2$) after 1 year of treatment. The eGFR was significantly higher in the LdT therapy group than in the ETV group after 6 months ($RR = 4.63$, $95\%CI: 0.73-8.54$, $Z = 2.33$; $P = 0.02$) 1 year ($RR = 3.35$, $95\%CI: 1.18-5.52$, $Z = 3.02$; $P = 0.002$) and 2 years ($RR = 11.00$, $95\%CI: 4.84-17.15$, $Z = 3.50$; $P = 0.0005$) of treatment.

Conclusion: Our meta-analysis of current evidence demonstrated that in CHB patients with impaired renal function, LdT could be the better choice than ETV.

Background

Hepatitis B virus (HBV) infection is a serious public health problem all over the world, approximately 257 million persons, or 3.5% of the population, were living with chronic HBV infection worldwide [1]. It is also respected to its complications, including liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality [2, 3].

Treatment's primary target in CHB is to prevent disease progression into serious complications by inhibiting of hepatitis B virus (HBV) DNA replication [4]. To date, six nucleos(t)ide analogs (NAs) are used in CHB treatment, including three nucleoside analogs: lamivudine [LAM], telbivudine [LdT], and entecavir [ETV]; and three nucleotide analogs: adefovir dipivoxil [ADV], tenofovir disoproxil [TDF] and tenofovir alafenamide (TAF). These antiviral agents usually have relatively strong antiviral potency and low incidences of Resistance. However, they can also potentially cause serious adverse events, such as myopathy, neuropathy, lactic acidosis, and renal dysfunction [5]. Among the adverse events, renal dysfunction is one of the risk factors, particularly in patients who already have renal impairment [6, 7].

Chronic HBV infection may cause renal dysfunction through immune complex-mediated glomerular diseases. As renal excretion is the primary route of elimination of the mainstay of CHB therapy [7], nucleos(t)ide may also induce kidney toxicity through various mechanisms, such as renal tubular injury, apoptosis, and mitochondrial toxicity [8].

Due to renal function is frequently impaired in patients with compensated CHB and patients usually require long-term treatment[2, 8],When choosing an appropriate antiviral medicine,nephrotoxicity,which marked by a decrease in estimated glomerular filtration rate(eGFR),should be particularly considered[9].Among NAs,Telbivudine (LdT) and Entecavir (ETV) are regarded as first-line antiviral agent in CHB patients with renal impairment.

Telbivudine and entecavir are used widely to inhibit hepatitis B virus (HBV) replication.However, Data comparing renal safety of these two antiviral agents in CHB patients with renal impairment are limited and lack systematic evidence base.Therefore,the main objective of this study is collate all available evidence and summarize the data to assess the renal safety of the nucleoside analogs LdT and ETV in this specific population.

Methods

Search strategy

PubMed, Web of Science, Scopus,Cochrane Library,ClinicalTrials.gov and CNKI (China National Knowledge Infrastructure) were searched without language restriction to identify relevant articles published from January 1, 2010 to February 1, 2020. The search was performed with the following keywords:‘chronic hepatitis B’,‘telbivudine’, ‘entecavir’,‘nucleos(t)ide Analogues’,‘renal Function’‘estimated glomerular filtration rate’,and their synonyms and related terms.

Selection Criteria

The following inclusion criteria were used to select studies for review:

1. Randomized controlled trials (RCTs), retrospective and prospective cohort studies.All studies had proper clinical information.
2. Study populations involving patients with chronic hepatitis B and renal impairment [eGFR between 30 and 90 mL/min/1.73 m²],and the results contained at least eGFR outcomes.
3. The study including a LdT group or ETV group.

The exclusion criteria were as follows:

1. The patients were coinfectd with either hepatitis A, C, D, or E virus or with human immunodeficiency virus (HIV)..
2. The study without sufficient information.
3. The study interventions did not include either LdT or ETV.

Efficacy endpoints

The efficacy end-point was the change in estimated glomerular filtration rate (eGFR) from baseline,which was calculated by the Modification of Diet in Renal Disease (MDRD)[10].Most studies reported the renal

function outcomes at the time range from 6 month to 2 years follow-up,so the study efficacy endpoints were analyzed at a time point of 6 months,1 year and 2 years.

Data collection

Two authors independently searched literature and extracted data using a predesigned data collection template, and discrepancies were discussed via discussion.The data were extracted for: (1) study characteristics:study design,year of publication,region, study type,Interventions,sample size and follow-up period.

(2) patient characteristics (age, gender) and baseline estimated glomerular filtration rate (eGFR);(3) study outcomes after treatment.The Inclusion and exclusion criteria were uniformly applied across all the publications.

Risk of bias

The Cochrane Collaboration Risk of Bias Tool was used to assess the risk of bias[11]. This tool comprised of seven criterias:(1)Random sequence generation;(2)Allocation concealment;(3)Blinding of participants and personnel;(4)Blinding of outcome assessment;(5)Incomplete outcome data;(6)Selective reporting;(7)other bias.

Three levels were used to assess the methodological quality:(1)low risk of bias;(2)high risk of bias;(3)unclear risk of bias.Assessment was independently performed by two authors, and disagreements were resolved via discussion.

Data analyses

All statistical analysis was conducted using Review Manager version 5.3 (The Cochrane Collaboration, Oxford, UK).For each eligible study, the dichotomous data were presented using the relative risk(RR) with a 95% confidence interval (95% CI),while continuous data were presented using the weighted mean difference (WMD).

The statistical heterogeneity between studies was assessed by using the chi-square (χ^2) and I-square (I^2) tests.,with significance set at $P < 0.05$,When $I^2 > 50\%$, $P < 0.05$ was considered to be statistically significant, and the random effects model was adopted for meta-analysis; otherwise,the fixed effects model was adopted[11, 12]

Results

Literature search

The study selection process is summarized in Figure 1.We identified 6102 relevant studies though database searches,After the initial screening and eligibility assessment phase,1972 redundant publications were excluded and, after referring to the titles and abstracts,a further 41 studies that not fulfilling the inclusion criteria were rejected. The remaining 4 studies without sufficient data were rejected,

Finally, 7 studies were enrolled in this meta-analysis. Five of the articles were retrospective cohort analyses [13-17] and two were RCTs [18, 19]. A total of 1088 patients, 522 of whom were treated with LdT and 566 with ETV were included in this meta-analysis. The LdT dose used in the studies was 600 mg/day and that of ETV was 0.5 mg/day.

Study characteristics

Table 1 summarizes the basic characteristics of the included studies and patients. Three of the included studies were from mainland China [13, 16, 19]. {Liu, 2019 #27; Yan, 2012 #37; Qi, 2015 #47} two studies from Taiwan, China [14, 15], one study from Korea [17] and one study from worldwide [18]. The included studies were published between 2010 and 2020. The sample size for each study ranged from 41 to 503. The mean age of the patients was 46.96 years (ranged from 38.3 to 55.2 years old). The duration of follow-up ranged from 1 year to 5 years. Male patients accounted for approximately 70.2% (ranged from 66.7% to 77%) of all patients. Two publications [14, 15] reported by the same first author were confirmed not to overlap due to the use of different study periods, so they were included in the study.

Table 1 Characteristics of included studies

Study Design	Year	Region	Study type	Interventions	Sample size	Men sex (%)	Agea (years)	Follow-up period
Liu et al.	2020	China	Cohort	LdT/ETV	LdT: 21 ETV:20	66.7%	38.25	1.5 years
Tsai et al.	2016	Taiwan	Cohort	LdT/ETV/TDF	LdT:42 ETV:62 TDF:37	77%	55.2	2 years
Tsai et al.	2015	Taiwan	Cohort	LdT/ETV/TDF	LdT:79 ETV:119 TDF:75	71.7%	52.9	5 years
X. Qi et al.	2015	China	Cohort	LAM/ADV/LdT/ETV	LAM:11 ADV:17 LdT:8 ETV: 20 Untreated:6	73%	42	2 years
Lee et al.	2015	Korea	Cohort	LdT/ETV	LdT: 61 ETV: 310	67.0%	53.8	1.5 years
Gane et al.	2013	Worldwide	RCT	LdT/LAM	LdT: 261 LAM: 242	NA	NA	2 years
Han et al.	2012	China	RCT	LdT/ETV/ADV	LdT: 50 ETV:35 ADV:30	69%	39.6	1 year

Changes in eGFR with LdT therapy

Six included studies, involving 514 patients, reported the change in eGFR after 1 year of LdT treatment (Fig. 2). The results showed that the eGFR was improved by 7.02 mL/min/1.73 m² with LdT after 1 year of treatment. There was statistical heterogeneity was observed among these studies ($I^2 = 85\%$, $P < 0.00001$) with a random-effects model. The result indicated a statistically significant change in the eGFR significant (RR = 7.02, 95%CI: 2.69–11.35, $Z = 3.17$; $P = 0.001$).

Changes in eGFR with ETV therapy

Five included studies, including 546 patients, investigated the change in eGFR after 12 months of treatment with ETV (Fig. 3). The results showed that the eGFR was slightly increased after ETV treatment compared with baseline (1.72 mL/min/1.73 m²), and there was no significant heterogeneity among these studies ($I^2 = 43\%$, $P = 0.14$) with a fixed-effect model. The overall test result indicated that the eGFR was slightly increased after 12 months of treatment with ETV (RR = 1.72, 95%CI: 0.09–3.35, $Z = 2.07$; $P = 0.04$).

Renal safety comparison between LdT therapy group and ETV therapy group

There is no significant differences in baseline demographic data (age, gender) and eGFR level between the study groups. Two studies comprising 412 patients reported the change in eGFR after 6 months of treatment, as shown in Figure 4a, The eGFR was significantly higher in the LdT therapy group than in the ETV group after 6 months (RR = 4.63, 95%CI: 0.73–8.54, $Z = 2.33$; $P = 0.02$). and there was no significant heterogeneity among these studies ($I^2 = 0\%$, $P = 0.95$) with a fixed-effect model. Five studies comprising 788 patients reported the change in eGFR after 1 year of treatment, as shown in Figure 4b, The eGFR was significantly higher in the LdT therapy group than in the ETV group after 1 year (RR = 3.35, 95%CI: 1.18–5.52, $Z = 3.02$; $P = 0.002$). and there was no significant heterogeneity among these studies ($I^2 = 0\%$, $P = 0.82$) with a fixed-effect model. Three studies comprising 284 patients reported the change in eGFR after 2 year of treatment, as shown in Figure 4c, The eGFR was significantly higher in the LdT therapy group than in the ETV group after 2 year (RR = 11.00, 95%CI: 4.84–17.15, $Z = 3.50$; $P = 0.0005$). and there was significant heterogeneity among these studies ($I^2 = 53\%$, $P = 0.12$) with a random-effects model. The changes trends in eGFR during treatment in the LdT and ETV groups are shown in Fig.5.

Risk of bias

All trials were evaluated by the Cochrane Collaboration's risk-of-bias tool. The risk of bias assessment conducted for each study included is presented in Fig. 6.

Discussion

Renal function is an important prognostic factor in CHB patients. Amet et al reported that 64.6% of patients were found to have renal abnormalities by international definition[20]. The study by Raquel et al demonstrated that the percentage of Renal and urinary disorders with LAM, ETV, LdT, ADV, TDF, and TAF were 0.02%, 1.6%, 0.1%, 0.4%, 6.8% and 11.1%[21]. The risk factors for renal abnormalities include aging, gender, smoking, alcohol intake, diabetes, hypertension, anaemia and dyslipidaemia[20, 22, 23]. so they recommend appropriate on-treatment monitoring of renal function[20]. All currently available NAs are primarily predominantly eliminated unchanged in urine. These oral Antiviral agents, especially the nucleotide analogs, are associated with a dose-dependent nephrotoxicity, and both of pre-existing renal insufficiency and concomitant nephrotoxic agents are considered to be the risk factors of nephrotoxicity[24]. Therefore, Special attention should be given to patients with pre-existing renal insufficiency who have been treated with Nucleos(t)ide Analogues, because they have a high tendency to develop renal dysfunction during prolonged CHB therapy[25].

We found that there's significant difference in comparing telbivudine with entecavir from 6 months to two years follow up period. Previous studies indicated that the improvement in eGFR was maintained long-term in telbivudine therapy[16, 18]. However, the mechanism by which telbivudine therapy improves renal function is still under investigation, it perhaps due to suppress ACE levels, which can control renin-angiotensin aldosterone regulatory system and affect systemic vasoconstriction and renal sodium and renal fluid retentions. Liang et al. reported that after about 1 year telbivudine treatment, Patients' eGFR was found significant increase. The serum angiotensin converting enzyme levels were negatively correlated with eGFR ($r = -0.375$, $p = 0.002$). Significant decreases of the serum angiotensin converting enzyme levels were also observed upon entecavir treatment, but no significant correlation was found between serum serum angiotensin converting enzyme levels and eGFRs ($r = -0.239$, $P = 0.138$)[26].

Some previous studies reporting that there was no obvious difference in mean eGFR among patients treated with entecavir[24, 27], some studies indicated that eGFR in CHB patients improved significantly after entecavir treatment, specially in renal patients[14, 15]. Mandíková J demonstrates that the potency of ETV to cause nephrotoxicity and/or clinically significant drug-drug interactions related to the tested transporters is considerably lower than that of nucleotide analogs[9]. One thing for sure is that the ETV-treated did not deteriorate significantly compared to baseline.

Tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, has been shown to have a potential nephrotoxic[25]. There is also study found that patients treated with TDF were not associated with renal impairment than patients treated with entecavir, but pre-existing renal insufficiency can increase the risk of developing changes in renal function[28]. However, tenofovir alafenamide (TAF), a new tenofovir salt formulation, was shown to have better renal and bone safety than TDF[29], can be used as a replacement drug. Patients who have been treated with TDF, especially in who with a baseline eGFR of below 90 mL/min, can switch TAF to improve renal function[29, 30]. However, the number of patients receiving with TAF is too small to consolidate that TAF has a less impact on renal function than TDF.

There were none of network Meta-analysis published focusing on renal safety of antiviral therapy of CHB patients with renal impairment. Also, there were several limitations in this study. First, the numbers of studies were modest, only seven researches were included in the meta-analysis, and the number of prospective studies is also limited. Second, most studies were retrospective cohort studies and observational, with only two RCT, so there is an increased selection bias risk in retrospective studies. Third, eGFR was evaluated after only 2 year. As the duration of treatment of patients with CHB is several years, the clinical significance of the reported eGFR changes needs further elucidation. Finally, the participants covered in our meta-analysis are mainly from Asian countries, where the prevalence of HBV infection is high, and this might limit the generalizability of the results to multiple ethnicities.

Conclusions

In conclusion, this meta-analysis current evidence demonstrated that compared with ETV therapy, LdT has a significant improvement in eGFR in CHB patients with renal impairment. Patients with renal impairment in particular benefited from telbivudine therapy. So in these patients, LdT could be the better choice than ETV.

Abbreviations

CHB: chronic hepatitis; LDT: telbivudine; ETV: entecavir; CNKI: China National Knowledge Infrastructure; HBV: Hepatitis B virus; HCC: hepatocellular carcinoma; NAs: nucleos(t)ide analogs; LAM: lamivudine; ADV: adefovir dipivoxil; TDF: tenofovir disoproxil; TAF: tenofovir alafenamide; eGFR: estimated glomerular filtration rate; RCTs: Randomized controlled trials; HIV: human immunodeficiency virus; MDRD: Modification of Diet in Renal Disease;

Declarations

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Not applicable.

Authors' contributions

BH planned the study. BH and SM collected intellectual materials, analyzed the data and drafted the manuscript. JW was involved in revising the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The data used to support the findings of this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the manuscript for publication.

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Figures

Figure 1

Flow chart of study selection for the meta-analysis.

Figure 2

The change in eGFR after 1 year of telbivudine treatment

Figure 3

The change in eGFR after 1 year of entecavir treatment

(a)

(b)

(c)

Figure 4

(a)The change in eGFR after 6 months of treatment comparing telbivudine with entecavir;(b)The change in eGFR after 1 year of treatment comparing telbivudine with entecavir;(c)The change in eGFR after 2 years of treatment comparing telbivudine with entecavir

(a)

(b)

Figure 5

Figure 5 (a) The changes trends of renal function during treatment in the LdT; (b) The changes trends renal function during treatment in the ETV.