International Immunopharmacology 42 (2017) 168–175

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis

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ARTICLE INFO

Article history:
Received 15 August 2016
Received in revised form 9 October 2016
Accepted 21 November 2016
Available online 1 December 2016

Keywords:
Chronic hepatitis B
CHB
HBV
Entecavir
Tenofovir
Efficacy
Safety

ABSTRACT

Background: The purpose of this study was to assess the efficacy and safety between tenofovir and entecavir in the treatment of CHB and HBV related cirrhosis through Meta-analysis. Methods
The electronic databases of PubMed, the Cochrane Library, Nature, CNKI and WanFang data were searched. The key words were: ("tenofovir", "entecavir") and ("Chronic Hepatitis B" or "CHB") and "Liver cirrhosis". Heterogeneity and report bias were analyzed.
Results: There was significant difference of ALT norm level in the short-term period of 3 months (RR = 1.43, 95%CI: 1.06–1.94, P < 0.017) and 6 months (RR = 0.89, 95%CI: 0.81–0.97, P < 0.017), and significant difference of undetectable HBV-DNA only in 3 months follow-up period (RR = 1.59, 95%CI: 1.04–2.42, P < 0.017) between TDF and ETV, but no significant difference in the long-term period. There is significant difference between TDF and ETV in eGFR level (RR = 1.601, 95%CI: 1.035–2.478, P = 0.0034) and hypophosphatemia incidence (RR = 4.008, 95%CI: 1.485–10.820, P = 0.006).
Conclusion: TDF has a better efficacy than ETV in 3 months treatment duration, but intriguingly, TDF might not better than ETV during the 6 months treatment period in the viral suppression and liver function improvement. There's no significant difference between TDF and ETV in the long-term treatment duration and in the treatment of HBV related liver cirrhosis. Both TDF and ETV could influence renal function but patients under TDF therapy may have more risk to suffer from renal damage and hypophosphatemia.

1. Introduction

Hepatitis B virus (HBV) infection will cause chronic hepatitis B (CHB), a difficult problem for centuries. The earliest human virus isolation known so far was obtained by laparoscopic liver biopsy from a Korean mummy in the sixteenth century [1]. And to date, HBV infection has already become a global problem. Till 2010, 248 million individuals have been reported the hepatitis B surface antigen (HBsAg) positive, and despite the availability of an effective vaccine, the virus causes about 780,000 deaths every year [1,2]. HBV carriers present a broad spectrum ranging from asymptomatic carrier state to liver cirrhosis and hepatocellular carcinoma [3]. It's estimated that about 15% to 30% of chronic hepatitis B virus (HBV) carriers in the world are at the increasing risks for developing liver cirrhosis and complicated end-staged liver disease [4].

The approved and widely used agents to treat CHB are conventional interferon alfa and pegylated interferon-alfa-2a as well as the nucleoside analogs (lamivudine, entecavir, and telbivudine) and the nucleotide analog (adefovir, dipivoxil and tenofovir) [5]. Evidence shows that entecavir and tenofovir have low incidence of drug-resistant mutants and side effects, moreover, the current guidelines recommend that the most common potent drugs to treat CHB and liver cirrhosis are nucleoside analog entecavir (ETV) and the nucleotide analog tenofovir (TDF) [6,7]. However, the difference of efficacy and the safety between ETV and TDF is under debating. And which one is the best to treat CHB and CHB related cirrhosis in different treatment duration remains unclear. Besides, whether there's any difference regarding the safety between TDF and ETV is not well concluded.

Therefore, the study aims to evaluate the efficacy and safety between tenofovir and entecavir in the treatment of CHB and HBV related cirrhosis through Meta-analysis.

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http://dx.doi.org/10.1016/j.intimp.2016.11.022
1567-5769/

2. Method and material

2.1. Article retrieval

The retrieval sources include PubMed, the Cochrane Library, Nature, China National Knowledge Infrastructure (CNKI) and WanFang Data. The key words were the combination of ("Tenofovir" and "Entecavir") and ("Chronic Hepatitis B" or "CHB") and "Liver cirrhosis". All human studies were included and no publish time lower limit (up to May 12, 2016) was taken. We also searched articles through relevant citations in related literature.

2.2. Inclusion and exclusion criteria

Any article which conforms to the under-mentioned criteria would be brought into our analysis: (1) The studies were randomized clinical studies (RCT) or cohort studies (retro-/prospective cohort). (2) The studies made the comparisons between ETV and TDF in the treatment of CHB patients. (3) Individuals were well represented CHB patients and without liver transplantation, hepatocellular carcinoma (HCC), or other desperate conditions. Besides, any articles with one of the following characteristics were also brought into the analysis: (1) The studies focused on TDF or/and ETV in the treatment of HBV related liver cirrhosis patients. (2) The studies included the safety information of TDF and ETV.

Any article which met one of the following conditions would be excluded: (1) case report, reviews, systematic reviews and Meta-analysis. (2) ETV and TDF combine therapy. (3) Data deficiency. (4) Animal studies. (5) Case-control study and cross-sectional study.

2.3. Quality assessment

We used the Cochrane Risk of Bias assessment tool in the software of Review Manager 5.3 for RCTs, and the Newcastle-Ottawa Scale (NOS) [8] for cohort studies for the assessment of each study's quality.

2.4. Data extraction

We extracted the following data from original articles: the first author's name, year of publication, patients' country of origin, study design, sample size, gender ratio, average age and standard deviation (SD), intervention treatment, treatment duration as well as the number of patients who appeared endpoints outcomes (indicators of therapeutic effects and treatment safety for HBV patients and liver cirrhosis patients). The extraction of all data was processed with Microsoft office Excel 2007.

2.5. Endpoint outcomes

After we analyzed the characteristics of all included articles, because of the widely reported from original articles, the measurements of efficacy were considered: 1) the numbers of patients who reached the normalized serum alanine aminotransferase levels (ALT norm) after treatment as the primary outcome to combine; 2) the occurrence rate of patients who reached the undetectable levels of HBV-DNA as the secondary outcome to combine.

In the comparison of TDF and ETV in HBV related liver cirrhosis patients, except ALT norm level and the undetectable levels of HBV-DNA, the new cases number of HCC and death cases number under ETV or/and TDF treatment were the outcome indicators of clinical results in order to reflect whether there's difference between TDF and ETV in preventing the terminal condition of liver cirrhosis.

The occurrence rate of patients' eGFR level under the specified low limit level of eGFR at end point (<60 mL/min or <50 mL/min) was the primary outcome to reflect the situation of renal damage. And the incidence rate of the decrease of eGFR from baseline was used as the secondary outcome to reflect the influence of TDF and ETV in renal function but not renal damage. Hypophosphatemia was another indicator to reflect pharm safety.

2.6. Statistical analysis

We performed a subgroup analysis in order to reflect the efficacy of ETV and TDF in different duration of treatment. I^2 was used to quantify the heterogeneity. If I^2 was >50, that suggests the existence of heterogeneity, the fixed effect model would be used to combine data; otherwise, it would be random effect model. Sensitivity analysis was performed to evaluate the stabilization of outcomes and find out whether there's a study which contribute to a biased result or high heterogeneity.

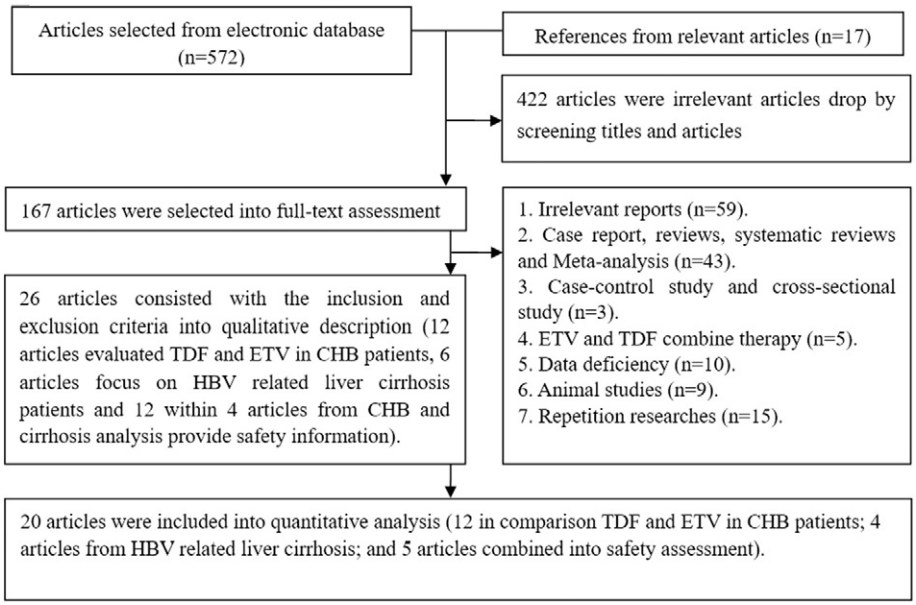

Fig. 1. Details of article retrieval.