

INPLASY PROTOCOL

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Comparative efficacy of the front-line anti-HBV drugs in nucleos(t)ide analogue-naive chronic hepatitis B, A protocol for systematic review and network meta-analysis

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ABSTRACT

Objective: To systematically evaluate the efficacy and safety of TAF, TDF and ETV in nucleos(t)ide analogue-naive Chronic Hepatitis B. Compare the efficacy of several drugs by sorting them.

Condition being studied: Chronic hepatitis B (CHB) is indicated when there is continued positivity for the hepatitis B virus (HBV) and the course of the disease exceeds half a year or the date of infection is not known, with clinical manifestations of the disease. According to the World Health Organization report, more than 2 billion people have been infected with HBV worldwide, and approximately 240 million of them are chronically infected. CHB is difficult to cure, TDF, TAF, ETV and LAM are all widely used. (TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide fumarate ETV: entecavir LAM: lamivudine).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 March 2020 and was last updated on 29 March 2020 (registration number INPLASY202030016).

INTRODUCTION

Objectives / Review question: To systematically evaluate the efficacy and safety of TAF, TDF and ETV in nucleos(t)ide analogue-naive Chronic Hepatitis B.

Compare the efficacy of several drugs by sorting them.

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(HBV) and the course of the disease exceeds half a year or the date of infection is not known, with clinical manifestations of the disease. According to the World Health Organization report, more than 2 billion people have been infected with HBV worldwide, and approximately 240 million of them are chronically infected. CHB is difficult to cure, TDF, TAF, ETV and LAM are all widely used. (TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide fumarate ETV: entecavir LAM: lamivudine).

METHODS

Participant or population: Patients with definite CHB and no prior experience with nucleos(t)ide analogue therapy were included. The following patients were excluded: patients who were infected with HIV or other hepato-tropic viruses; those who had drug-induced liver diseases, alcoholic liver disease or autoimmune liver diseases, tumors, serious complications in the heart, kidney, brain and other organs; and patients who were in pregnant or lactating.

Intervention: In the TAF group, the enrolled patients were given the conventional dosage of tenofovir 25 mg/day orally. In the TDF group, the enrolled patients were given the conventional dosage of tenofovir 300 mg/day orally. In the ETV group, the enrolled patients were given the conventional dosage of entecavir 500 mg/day orally.

Comparator: In the LAM group, the enrolled patients were given the conventional dosage of entecavir 100 mg/day orally. In the ADV group, the enrolled patients were given the conventional dosage of entecavir 100 mg/day orally. In the PLA group, the enrolled patients were given placebo once daily orally.

Study designs to be included: Randomized controlled trials(RCTs).

Eligibility criteria: Studies will be selected according to the PICOS criteria(Participant, Intervention, Comparator, Outcomes, Study design) outlined in the referred sections.

Search strategy: #1 Entecavir[Title/Abstract] OR Baraclude[Title/Abstract] #2 "Tenofovir"[Mesh] #3 Tenofovir[Title/Abstract] OR 9 - (2 - Phosphonylmethoxypropyl)adenine[Title/Abstract] OR 9 - (2 - Phosphonomethoxypropyl)adenine[Title/Abstract] OR Viread[Title/Abstract]#4 "Lamivudine"[Mesh] #5 Lamivudine[Title/Abstract] OR BCH-189[Title/Abstract] OR GR-109714X[Title/Abstract] #6 "adefovir" [Supplementary Concept] #7 adefovir[Title/Abstract] OR 9-PMEA[Title/Abstract] OR 9 - (2 - phosphonylmethoxyethyl)adenine[Title/Abstract] #8 "Hepatitis B, Chronic"[Mesh] #9 Hepatitis B, Chronic[Title/Abstract] OR Chronic Hepatitis B Virus Infection[Title/Abstract] OR Hepatitis B Virus Infection, Chronic[Title/Abstract] OR Chronic Hepatitis B[Title/Abstract] #10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9).

Information sources: We will search publications through Apr 2020 using the following databases: Web of Science, PubMed, the Cochrane Library, EMBASE and Clinical Trials. The retrieval strategy is in English, and if the retrieved literature is not in English and could be read by the team through translation, such articles will be included in this study. The search terms included "Tenofovir", "Entecavir", and "Hepatitis B, Chronic". Grey literature was not included in this study.

Main outcome(s): Normalized ALT. After a period of treatment, ALT level of patients reduced to normal. The definition of normal is defined by the instruments used in each study, with a few gaps between each instrument.

Additional outcome(s): 1. Virological response. It means that the laboratory instrument failed to detect the amount of virus. Only PCR results are included in this study. This study is not limited to units, either UI/ml or copies/ml. The instrument sensitivity of early tests was lower than that of recent ones. 2. Laboratory abnormalities any Grade 3 or 4. The study

does not limit the number of laboratory tests.

Data management: ADDIS 1.16.5 software will be used for the network meta-analysis. The network evidence plots will be drawn by the STATA 16 software. The funnel plot is drawn by STATA software.

Quality assessment / Risk of bias analysis: The risk of bias in the included studies will be assessed using the RCT bias risk assessment tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions (5.1.0).

Strategy of data synthesis: The dichotomous variables are expressed as the relative risk (RR) as an effect indicator, and the estimated value and 95% confidence interval (CI) will be included as effect analysis statistics. The random effect model will be used in this network meta-analysis. Consistency analysis is done through Node-split analysis. If an inconsistency occurs, the cause should be identified and explained and analyzed. The significance level will be set at $\alpha=0.05$.

Subgroup analysis: We will set up subgroups according to the situation of HBeAg. Each subgroup analyzed normalized ALT and virological responses.

Sensitivity analysis: We will conduct sensitivity analysis based on study quality.

Countries involved: China.

Other relevant information: The purpose of this study will be to compare the efficacy and safety of TAF, TDF and ETV. However, if only pairwise comparison will be conducted, few literatures are retrieved. Therefore, LAM, ADV and PLA will be introduced into this study for comparison, and direct and indirect comparison will make the conclusion more convincing. In the discussion, TAF, TDF and ETV will be still the focus of analysis.

Keywords: Tenofovir; Entecavir; Hepatitis B, Chronic; Nucleos(t)ide Analogue-naïve; Network Meta-Analysis.