INPLASY

The efficacy and safety of oral hepatoprotective agents combined with entecavir in the treatment of chronic hepatitis B: a network meta-analysis

INPLASY2023110024

doi: 10.37766/inplasy2023.11.0024

Received: 06 November 2023

Published: 06 November 2023

Zhu, BQ[1]; Tao, X[2]; Wei, YK[3]; Hu, JQ[4]; Yang, SY[5]; Zhang, MM[6]; Tong, RS[7]; Ye, Y[8]; Long, EW[9].

Corresponding author:
Enwu Long

dragon984169@126.com

Author Affiliation:
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital.

ADMINISTRATIVE INFORMATION

Support - This paper was funded by Key Basic Research Projects of the Basic Strengthening Plan (2023-JCJQ-ZD-118-00), Sichuan Provincial Department of Science and Technology (2021YFS0197).

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023110024

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 November 2023 and was last updated on 06 November 2023.

INTRODUCTION

Review question / Objective We aim to evaluate the efficacy and safety of different types of hepatoprotective agents combined with entecavir in the treatment of chronic hepatitis B.

Rationale Hepatoprotective agents refer to drugs that have the effects of improving liver function, promoting liver cell regeneration, and/or enhancing liver detoxification function. At present, the treatment of Chronic hepatitis B (CHB) mainly relies on antiviral drugs, but the therapeutic value of liver protective drugs has not been denied. relevant research results indicate that the use of hepatoprotective agents such as bicyclol, tiopronin, polyene phosphatidylcholine, silibinin, and glycyrrhetinic acid preparations effectively reduces liver enzyme levels and alleviates CHB related liver damage. Common oral liver protective drugs include: silymarin (capsules/tablets), bicyclol tablets, compound glycyrrhizin tablets, diammonium glycyrrhizinate (enteric-coated capsules/capsules); polyene phosphatidylcholine capsules; silibinin (meglumine tablets/capsules) and tiopronin tablets. As an auxiliary treatment for CHB, exploring the efficacy and safety of different types of hepatoprotective agents combined with antiviral therapy on patients' liver function levels and viral immune response will further promote the selection and application of hepatoprotective agents in clinical practice. Based on this, we aim to explore and analyze the efficacy and safety of the combination of oral hepatoprotective agents and entecavir in the treatment of CHB.

Condition being studied At present, there have been studies evaluating the efficacy and safety of different types of glycyrrhetinic acid preparations in

chronic hepatitis B[1]. However, glycyrrhetinic acid preparations are only one of the types of hepatoprotective agents, and other hepatoprotective agents are diverse and widely used. No research has systematically evaluated the efficacy and safety of different types of oral liver protective drugs as adjunctive antiviral drugs

[1]Gao W, Zhao Y, Guo L, Wang Y, Gong H, Zhang B, Yan M. Comparative effectiveness of glycyrrhizic acid preparations aimed at improving liver function of patients with chronic hepatitis B: A network meta-analysis of 53 randomized controlled trials. Phytomedicine. 2023 Jul 25;116:154883. doi: 10.1016/j.phymed.2023.154883. Epub 2023 May 18. PMID: 37224775.

METHODS

Search strategy We searched Chinese and English databases, including PubMed, Embase, Cochrane Library, Wanfang Database, China national knowledge internet (CNKI), and China biomedical literature service system (SinoMed), to collect randomized controlled trial (RCT) literature comparing the efficacy and safety of oral hepatoprotective agents combined with entecavir in the treatment of CHB. The search terms included: "glycyrrhizic acid" "bicyclol", "polyene photosphatidycholine", "tiopronin", "silymarin", "silibinin", "entecavir", "Hepatitis B, Chronic", "randomized", etc. We searched by using free words combined with subject words. The search was conducted from the establishment of the database until July 31, 2023.

Participant or population Patients diagnosed with CHB accompanied by liver dysfunction.

Intervention The intervention group should be treated with entecavir, and on the basis of antiviral therapy, a hepatoprotective agents should be used (including: silymarin capsules/tablets, bicyclol tablets, compound glycyrrhizin tablets, diammonium glycyrrhizinate enteric-coated capsules/capsules, polyene phosphatidylcholine capsules, silibinin meglumine tablets/capsules and tiopronin tablets). The combination of hepatoprotective agents and entecavir should last for more than 4 weeks. The treatment course, dosage form, and dosage should be consistent with the corresponding control group.

Comparator The control group should only use entecavir for treatment, and the treatment course, dosage form, and dosage should be consistent with the corresponding intervention group.

Study designs to be included 1) Patients diagnosed with CHB accompanied by liver dysfunction; 2) The experimental group were treated with a different type of hepatoprotective agent, combined with entecavir, while the control group was treated with entecavir alone; 3) The study included both the combination medication group and the monotherapy group for a duration of more than 4 weeks; 4) The study reported the following outcome indicators: ALT, AST, HBV DNA clearance rate, HBeAg clearance rate, and incidence of adverse drug reactions; 5) The research type is RCT.

Eligibility criteria Inclusion criteria: Chinese or English literature.Exclusion criteria: 1) Other literature types: including systematic reviews, guidelines, consensus, conference abstracts, animal experiments, reviews, non-randomized controlled trials, etc; 2) Literature unrelated to the topic; 3) Repeated research (only the most complete or recently published literature collected); 4) Diagnosis, intervention measures or treatment courses do not meet the inclusion criteria; 5) Unable to obtain basic patient information, medication status, outcome indicators, and other data; 6) Studies evaluating other diseases in CHB patients.

Information sources Chinese and English databases, including PubMed, Embase, Cochrane Library, Wanfang Database, China national knowledge internet (CNKI), and China biomedical literature service system (SinoMed).

Main outcome(s) We defined liver function indicators as the changes in ALT and AST compared to baseline to measure the recovery of liver function in CHB patients with abnormal liver function. The changes in ALT from baseline and AST from baseline are the primary outcome indicators. The above continuous variables are represented as mean difference (MD) and 95% confidence interval (CI).

Additional outcome(s) We defined the virus clearance indicators as the proportion of people who turned negative for HBV DNA and HBeAg at the endpoint compared to baseline. As binary variables, HBV DNA clearance rate, HBeAg clearance rate and incidence of ADR are represented by risk ratios (RR) and 95% CI.

Data management We searched relevant databases based on literature retrieval strategies, imported preliminary results into EndnoteX9, and deduplicated the literature. Using a back-to-back independent screening method with two

individuals, the literature is initially screened based on the title and abstract, excluding literature unrelated to the topic or inconsistent with the type. Afterwards, the article is rescreened by reading the entire text. If there is disagreement, a third-party researcher is requested to make a ruling.

Quality assessment / Risk of bias analysis We used the bias risk assessment tool provided in version 5.1.0 of the Cochrane handbook to evaluate the literature quality of the included RCTs, mainly including the following 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The measurement criteria for other biases are: whether there are differences in age, gender ratio, and disease course between the experimental group and the control group at baseline.

Strategy of data synthesis We used Review Manager 5.3 software to generate risk of bias graph. Statistical analysis was conducted by STATA 14.2. We constructed a network plot of intervention measures for each indicator. When evaluating heterogeneity, we used I^2 test: a fixed effects model was used when $I2 \leq 50\%$, and a random effects model was used when $I2 > 50\%$. If there is a closed loop in the network relationship graph, the inconsistency factor (IF) is used to evaluate the inconsistency between direct and indirect evidence, and a Z-test is conducted. If the lower limit of 95% CI for IF includes 0, and the P-value of the Z-test is greater than 0.05, it is considered that the circular inconsistency is not significant and can be analyzed using a consistency model.

Subgroup analysis In this study, we divided the study into two groups based on the duration of medication used by patients:≤6 months and >6 months, and conducted subgroup analysis.

Sensitivity analysis We conducted sensitivity analysis on ALT and AST indicators by using fixed effects models instead of random effects models. In the virus clearance rate indicators of this study, due to the small heterogeneity, we used fixed effects models for analysis.We used a random effects model for sensitivity analysis of HBV DNA clearance rate, and used odds ratio (OR) instead of RR to evaluate HBeAg clearance rate.

Language restriction Chinese or English literatures.

Country(ies) involved China.

Keywords chronic hepatitis B; hepatoprotective agents; efficacy; safety; network meta-analysis.

Contributions of each author

Author 1 - Baoqiang Zhu.
Email: zbq160911@163.com
Author 2 - Xue Tao.
Author 3 - Yuankui Wei.
Author 4 - Jiaqiang Hu.
Author 5 - Shiyu Yang.
Author 6 - Mingming Zhang.
Author 7 - Rongsheng Tong.
Author 8 - Yun Ye.
Author 9 - Enwu Long.