Evaluation of antiviral indications and therapeutic effect by liver biopsy combined with clinical trial parameters on chronic HBV infection with different transaminase levels

Study Protocol with Statistical Analysis Plan (SAP) and Informed Consent Form (ICF)

October 25, 2018

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Study Protocol

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Study Protocol

Study titled ‘Evaluation of antiviral indications and therapeutic effect by liver biopsy combined with clinical trial parameters on chronic HBV infection with different transaminase levels’was approved by the First Affiliated Hospital of Xi’an Jiaotong University of Medicine Clinical Researches Ethics Committee meeting on 10/19/2018 with approval number: XJTU1AF2018LSK-146.

The patients or legal representatives of the children who participated in the study were informed about the aim and the programs to be applied throughout the study.Volunteer Information Form has been signed and approved in accordance with the standards deemed appropriate by the First Affiliated Hospital of Xi’an Jiaotong University of Medicine Clinical Researches Ethics Committee (This form can be seen on Informed Consent Form (ICF) section). The study was conducted in accordance with the Declaration of Helsinki.

Hypothesis of the Study

H0:Initiating treatment is not recommend for the patients with ALT <2ULN, high viral load,because some studies considered that the potential harms of long-term therapy,including cost,low response rates,drug adverse effects and development of resistance,outweigh its benefits.

H1:Initiating treatment is recommend for the patients with ALT <2ULN,high viral load,because some studies considered that high levels of serum HBV DNA (>10^4copies/ml)are associated with a high risk of hepatocellular carcinoma (HCC) and the histological activity and HBV-specific immune responses do also occur in this

phase.

Inclusion Criteria

(1)Patients with a history of chronic HBV infections,defined as those in whom presence of serum hepatitis B surface(HBsAg) for more than 6 months.

(2)All patients had underwent a liver biopsy.

(3)All patients signed the informed consent.

(4)No history of interferon or Nucleoside analogue treatment.

Exclusion Criteria

(1)Co-infection with human immunodeficiency virus(HIV),hepatitis A virus(HAV),hepatitis C virus(HCV),hepatitis D virus(HDV) and/or hepatitis E virus(HEV).

(2)Decompensated cirrhosis.

(3)History of liver transplantation.

(4)History of hepatocellular carcinoma(HCC).

(5)Having received antiviral treatment.

(6)Taking immunoregulation drugs such as cytotoxic agents and hormones.

(7)Use of hepatotoxic drugs or regular consumption of alcohol.

(8)Autoimmune disease or antinuclear antibody titers higher than 1:160.

(9)And other chronic liver disease.

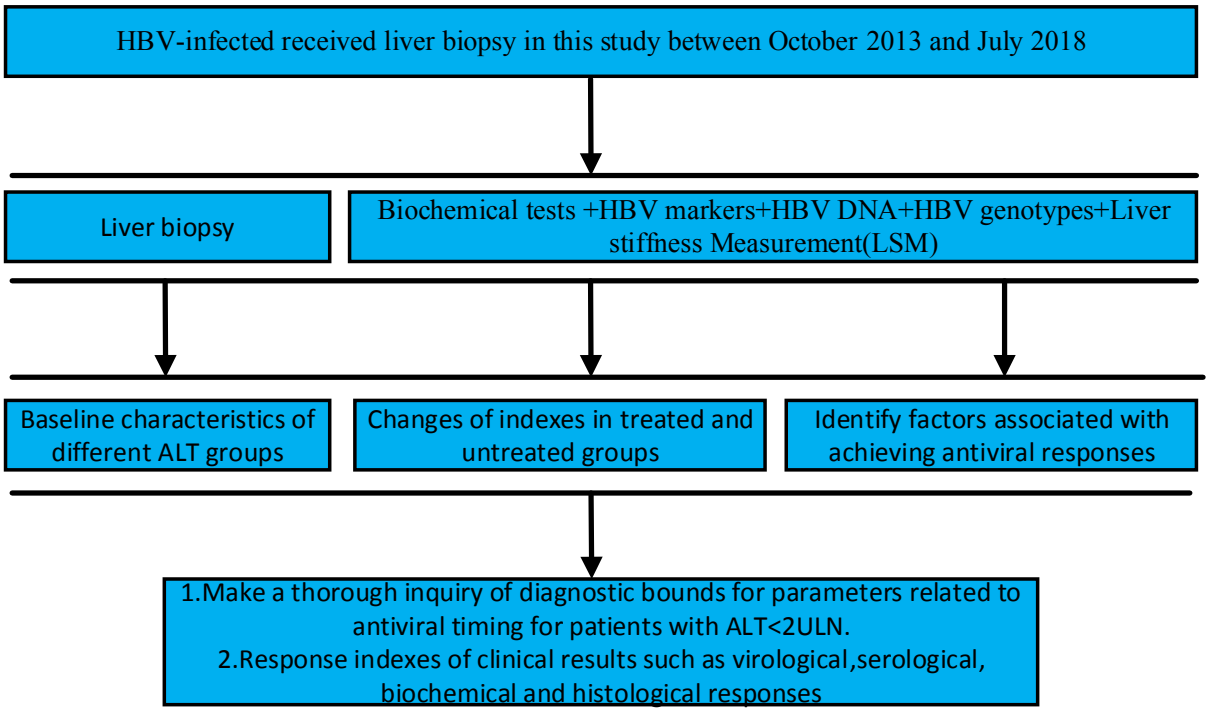
(10)Incomplete data.

Applied Evaluations

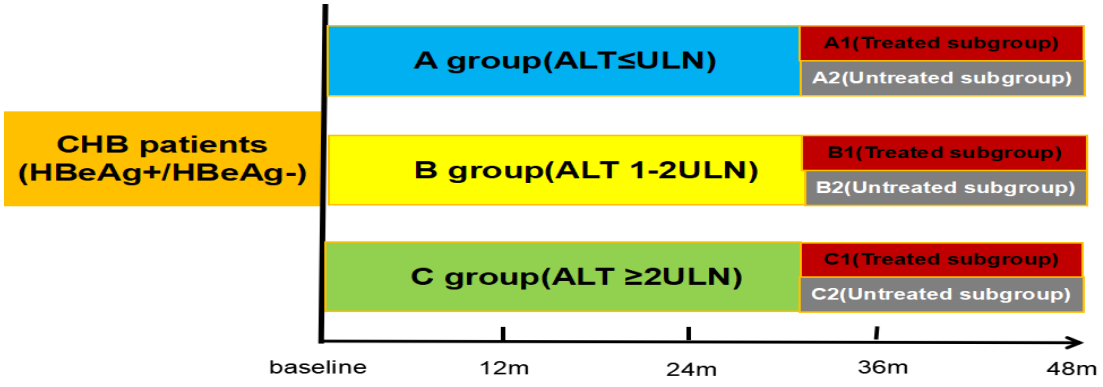
Response indexes as the follows: virological response(HBV DNA below the

detection limit);HBsAg response(HBsAg decline≥0.5log10 IU/ml);HBeAg seroconversion(HBeAg loss and HBeAb appearance);biochemical response(ALT normalization);LSM response(LSM decrease as at least a 1-kPa).

Research programme



Research group



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Statistical Analysis Plan (SAP)

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Statistical Analysis Plan (SAP)

The statistical program Statistical Package for Social Sciences (SPSS) Version 20.0(SPSS Inc., Chicago, IL, USA) was used in the data analysis of the study.The p value of $p<0.05$ was considered to be statistically significant in the data analysis. Continuous quantitative variables were expressed as mean±standard deviation (SD) for normal distributions or median and interquartile range (IQR)(25th-75th percentile) for abnormal distributions,which were assessed with an independent samples T test or the Mann-Whitney U test as comparison of two sets of samples while comparison of multiple samples were assessed with ANOVAs or Kruskal-Wallis tests.Repeated measures date of general linear model were used to calculate variation trend between treated and untreated follow-up patients. Categorical variables were expressed aspercentages that were analyzed using the χ^2 test, such as gender, HBV genotype,ALT, HBsAg, HBeAg, HBeAb, HBcAb and LSM.

The receiver operating characteristic (ROC) curve was plotted in order to find the most appropriate HBV DNA ,HBsAg, HBeAg cutoff value for diagnosis of patients with ALT<2ULN who are chronic HBV infection or chronic hepatitis B.

Univariate logistic regression and multivariate forward stepwise logistic regression were used to assess the incidences of antiviral responses, such as HBV DNA response, serological responses, biochemical response

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Informed Consent Form (ICF)

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Informed Consent Form (ICF)

Description of the Physiotherapist

This study is a retrospective observational cohort study,some baseline demographics and clinical data were obtained from the electronic integrated clinical records system.In consideration of achieving complete follow-up information, if you accept yourself or your child to be participated,it is a scientific research and it is titled as ‘Evaluation of antiviral indications and therapeutic effect by liver biopsy combined with clinical trial parameters on chronic HBV infection with different transaminase levels’,which aimed to explore the effect of antiviral therapy in CHB patients with these characteristics.All the patients are planed to achieve follow-up information at least 12 months and follow-up assessments such as HBV DNA,HBV Markers,liver function,LSM were performed at months 12, 24, 36 and 48.This research will be carried out by the department of the Infectious Disease,The Affiliated Hospital of Yan’an University and the First Affiliated Hospital of Xi’an Jiaotong University,Xi'an,China.

Benefits of participation in this study

Chronic HBV infection is a lifelong disease and high levels of serum HBV DNA (>10^4copies/ml)are associated with a high risk of liver cirrhosis and hepatocellular carcinoma (HCC).Therefore,the goal of antiviral therapy is to inhibit HBV replication in a sustained manner and to improve the quality of life and prolong the survival time.But the patients with ALT<2ULN are recommended follow-up and no need for antiviral therapy.Comprehensive assessment of the degree of liver inflammation and

fibrosis is conducive to the timely diagnosis of the patients and to determine whether the active anti-viral treatment.Through longitudinal follow-up of the clinical outcome of treated and untreated patients,further lay a theoretical foundation for whether such patients should be treated with antiviral therapy,so as to alleviate the psychological stress they have to endure because of the long follow-up waiting.It also avoids the waste of medical resources caused by improper treatment, and helps to alleviate the economic burden of patients, families and society.Therefore,it is important for these patients to particate in this study achieve individualized management scheme.

See the risks or inconveniences of this study and the compensatory measures

This subject is a retrospective study,so there is no direct conflict of security interests between the researcher and the participators.

Confidentiality of research

Your personal information collected in this study is confidential and only used for research and scientific analysis.By signing this informed consent,you can allow people with legitimate reasons to collect and view your personal data.

Your rights

The participation in the study is entirely voluntary, and you can withdraw at any stage of the study without any reasons,which will not affect your relationship with the medical staff and future treatment.

Finally,thank you for your great support for this study,and for your contribution to the exploration of the diagnosis and treatment of the disease.

Agree to declare

I have understood the purpose,process,potential benefits and possible adverse reactions of this study,volunteered to participate in the study and follow the research process as far as possible.

Name and the Surname of the Participant and Legal Representative:

Date: **Signature:**

Name and Surname of the Witness:

Date: **Signature:**