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Original article

Prevalence of mutations in HBV DNA polymerase gene associated with nucleos(t)ide resistance in treatment-naive patients with Chronic Hepatitis B in Central China

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ABSTRACT

Objective: There are a lot of disagreements in the studies on hepatitis B virus (HBV) DNA polymerase mutation rate associated with nucleos(t)ide analogues (NAs) in treatment-naive chronic hepatitis B (CHB) patients. This is the first study aimed to investigate the prevalence of spontaneous HBV resistance mutations in Central China.

Methods: This study included treatment-naive patients with CHB from June 2012 to May 2015 receiving care at the Institute of Liver Disease in Central China. All patients completed a questionnaire covering different aspects, such as family medical history, course of liver disease, medication history, alcohol use, among others. Mutations in HBV DNA polymerase associated with NAs resistance were detected using INNO-LiPA assay.

Results: 269 patients were infected with HBV genotype B (81.4%), C (17.9%), and both B and C (0.7%). Mutations in HBV DNA polymerase were detected in 24 patients (8.9%) including rtM204I/V ($n = 6$), rtN236T ($n = 5$), rtM250V ($n = 2$), rtL180M ($n = 2$), rtT184G ($n = 1$), rtM207I ($n = 1$), rtS202I ($n = 1$), rtM204V/I & rtL180M ($n = 5$), and rtM204I & rtM250V ($n = 1$).

Conclusion: Spontaneous HBV resistance mutations in HBV DNA polymerase were found in treatment-naive patients with CHB in Central China. These findings suggest that we should analyze HBV DNA polymerase resistance mutation associated with NAs before giving antiviral therapy such as lamivudine (LAM), adefovir (ADV), and telbivudine (LdT).

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Introduction

Infection with hepatitis B virus (HBV) can cause severe diseases such as liver cirrhosis and hepatocellular carcinoma (HCC), with approximately one million deaths annually around the world.[1] Nucleos(t)ide analogues (NAs), including lamivudine (LAM), adefovir (ADV), telbivudine (LdT), entecavir (ETV), and tenofovir (TDF) were recommended by international guidelines for suppressing HBV replication, and have been shown to decrease the rate of complications.[2–4]

Despite high drug efficacy for inhibiting HBV, one of the largest obstacles with long-term NAs therapy is the development of viral resistance. LAM, used widely as the first NA, has the highest viral resistance rate of 70% after five years of therapy.[5] ADV and LdT are superior to LAM for their lower prevalence of viral resistance, while ETV and TDF effectively suppress HBV DNA replication with minimum drug resistance.[6] NAs treatment failure has been linked to mutations at the reverse transcriptase (rt) region of the HBV DNA polymerase gene, and mutations at individual codons in the HBV polymerase gene conferring resistance to different NAs. For example, rtM204V/I pathway is responsible for the resistance to L-NAs, such as LAM, LdT, clevudine (CLD), and ETV. Also, rtN236T pathway could confer ADV and TDF resistance, and rtA181T/V pathway could affect LAM, ADV, LdT, and TDF efficacy.[5,7,8]

It has been found that natural HBV reverse transcriptase mutations exist even in treatment-naive patients with CHB from Europe, Asia, and the Middle East, but the prevalence vary from 0% to 57%.[9–13] This wide range might be caused by different study designs, regions, ethnicities, mutation detection methods, sample sizes, and so on. Using a systematic review and meta-analysis, Zhang et al.[13] found an 8.0% prevalence of total and primary mutations among untreated CHB patients in China, and that Southern China had a little higher pooled total mutation rate of 8.22% than Northern China 7.55%. Therefore, it is important to understand the true prevalence of HBV DNA polymerase mutation analysis among treatment-naive patients with CHB in different areas of China, because most of them will be treated with NAs at first. To our knowledge, there has been no study in patients of Central China. The purpose of this study is to determine the prevalence and clinical characteristics of spontaneous mutations in Central Chinese cohort, and focus on clinically significant HBV DNA polymerase associated with NAs resistance mutations (rtM250V, rtN236T, rtM204V/I, rtS202I, rtA181T/V, rtT184G, rtL180M, and rtM/V207I) by using the sensitive INNO-LiPA assay.

Patients and methods

Patients

We performed a prospectively analysis of 269 patients with CHB of the Institute of Liver Disease, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan who had never received any anti-HBV treatment with NAs or interferon, between June 2012 and May 2015. Patients were included according to the following criteria – age 18 years or older, HBV DNA >100 IU/mL, positive hepatitis B surface antigen, history of HBV infection for more than 6 months. Patients co-infected with HCV, HDV, or HIV were excluded. The diagnosis of hepatitis was established by needle biopsy. Liver biopsies were performed under ultrasound guiding and histological grade (G) and stage (S) were evaluated. We collected patients of chronic HBV infection and divided them into four phases (immune tolerant phase, immune clearance phase, low or non-replicative phase, reactivation phase) by the standard of the Guidelines for Chronic Hepatitis B in China, version 2010. The informed consent was obtained from each patient enrolled in the study. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Hubei Provincial Hospital of Traditional Chinese Medicine.

Patient questionnaires

Questionnaires, including questions about family medical history, HBV infection and treatment history, other disease history, ethnicity, and drug and alcohol history were completed by all patients.

General laboratory tests

Markers of HBV infection were measured using the commercial kit of electro-chemiluminescence assay (Roche Diagnostics, Mannheim, Germany). HBV DNA was quantified using the Amplicon monitor assay (ABI, California, USA). ALT, AST, and GGT were determined using the commercial kit of ultraviolet absorption spectrophotometry assay (Roche Diagnostics, Mannheim, Germany).

HBV polymerase gene mutation and genotype by INNO-LiPA

HBV DNA polymerase mutations and genotypes were measured using the INNO-LiPA assay kit (Shenzhen, China). This assay detected mutations at codons 180, 181, 184, 202, 204, 207, 236, 250 of the HBV DNA polymerase gene, with a reported detection lower bound of 5% of the circulating viral load.

Statistical analysis

Results were reported as mean and standard deviation and/or median and range for continuous variables and percentages for categorical variables. The categorical data were compared between groups using the chi-square test or Fisher's exact test, and the normally distributed continuous variables were analyzed by the Student's *t*-test. The nonparametric variables were analyzed by the Mann–Whitney *U*-test. All *p*-values were two-tailed, and $p < 0.05$ was considered statistically significant. Data analysis was performed using the Statistical Package for Social Science version 19.0 (SPSS, Chicago, USA).

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