



Comparison of rescue strategies in lamivudine-resistant patients with chronic hepatitis B

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ABSTRACT

Lamivudine (LAM) resistance now poses a major problem in the management of patients with chronic hepatitis B virus (HBV) infection. We retrospectively collected clinical data on chronic HBV-infected patients who had developed LAM resistance under de novo LAM monotherapy and subsequently took nucleos(t)ide analogs as rescue strategy in our hospital. From initiation of rescue therapies to January 2012, incidence of antiviral drug resistance was 23.67%, 18%, 6.94% and 0% ($P = 0.007$) in the group of switching to adefovir dipivoxil (ADV) monotherapy, switching to entecavir (ETV) monotherapy, adding on ADV and switching to combination of ADV and ETV. At month 12, the median levels of serum HBV DNA were respectively 9300 IU/mL, 4648 IU/mL, 2054 IU/mL and 100 IU/mL ($P < 0.001$), and the cumulative rates of serum ALT normalization were respectively 75%, 84%, 93% and 100% ($P = 0.003$). Additionally, the strategy of switching to ADV monotherapy induced more single rtA181T mutations. In conclusion, switching to ADV monotherapy has been widely used in real-world clinical practice in China, however, due to the high incidence of drug resistance, switching to neither ADV nor ETV monotherapy is optimal when LAM resistance occurs; combination of ADV and ETV is most effective, whereas the strategy of adding on ADV is rational for most of LAM-resistant Chinese patients with chronic hepatitis B.

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1. Introduction

Hepatitis B virus (HBV) infection frequently leads to liver cirrhosis and hepatocellular carcinoma. The development of oral nucleos(t)ide analogs (NA) has substantial impact in the anti-HBV treatment. Nevertheless, the emergence of drug-resistant mutations within the viral reverse-transcriptase (RT) gene is the major drawback of NA treatment (Locarnini and Bowden, 2010). Because viral drug resistance is associated with rebound in viral load levels and the subsequent worsening of liver disease (Billioud et al., 2011), it is becoming clinically important to adjust antiviral therapy when viral drug resistance occurs.

Lamivudine (LAM) has been widely used as a first-line therapy for chronic hepatitis B (CHB). However, a major shortcoming of LAM is the frequent emergence of drug resistance mutations and it was reported that the cumulative incidence of LAM resistance after 1 year and 4 years respectively arrived at 24% and 66% (Lai

Abbreviations: HBV, hepatitis B virus; LAM, lamivudine; ADV, adefovir dipivoxil; ETV, entecavir; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase.

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et al., 2003; Leung et al., 2001). As rescue therapies, switching to adefovir dipivoxil (ADV) or entecavir (ETV) monotherapy and adding on ADV were once suggested against LAM-resistant HBV (Lee et al., 2012), but studies about the efficacy of switching to combination of ADV and ETV were few. Additionally, incidence of drug resistance after initiation of rescue therapies varied markedly between studies (Perrillo et al., 2011; Lee et al., 2009; Dai et al., 2007). The aim of this article is to investigate various rescue strategies in LAM-resistant patients with CHB in real-world clinical practice in China and compare the incidence of drug resistance among them.

2. Patients and methods

2.1. Patients

We retrospectively collected clinical data between September 2007 and January 2012 on chronic HBV-infected patients who had developed antiviral drug resistance under de novo LAM monotherapy and subsequently took nucleos(t)ide analogs as rescue strategy for at least 12 months in our hospital. Individual rescue therapy regimens were chosen based on attending physicians' own discretion. The observational endpoint for every patient was the emergence of antiviral drug resistance for the administered

Table 1
Primers used for HBV reverse-transcriptase gene amplification.

Polarity	Sequences (5'–3')	Position	Round
Sense	AGT CAG GAA GAC AGC CTAC TCC	3146–3167	First
Antisense	AGG TGA AGC GAA GTG CAC AC	1577–1596	
Sense	TTC CTG CTG GTG GCT CCA GTT C	54–75	Second
Antisense	TTC CGC AGT ATG GAT CCG CAG	1258–1278	

medications to January 2012. Antiviral drug resistance was defined as virological breakthrough (>1 log₁₀ increase in serum HBV DNA level from the nadir in a patient who had an initial virological response, Lok and McMahon (2007)) accompanied with documented genotypic resistance. Patients with hepatic decompensation, past or current hepatocellular carcinomas or liver transplantation were excluded. Other criteria for exclusion were infection with hepatitis A, C, D, E or HIV, or the presence of other forms of liver diseases such as autoimmune or alcoholic liver disease, drug hepatitis or Wilson's disease. Informed written consent for the analysis was obtained from each patient. The study was approved by the ethics committee of Beijing 302 Hospital.

2.2. Biochemical and serological markers and quantification of HBV DNA

Serum HBV DNA, ALT, HBeAg were routinely detected in the Central Clinical Laboratory of Beijing 302 Hospital. Among these, HBV DNA level was determined by a popular real-time quantitative PCR (qPCR) kit (Fosun Pharmaceutical Co., Ltd., Shanghai, China) with a lower detection limit of 100 IU/mL. The normalized level of serum ALT was ≤40 U/L.

2.3. HBV RT gene amplification and sequencing

HBV gene fragment (nucleotides (nt) 54–1278) encompassing the complete RT gene (nt 130–1161) was amplified by nested PCR. The sense and antisense primers for first-round PCR and second-round PCR were described in Table 1. The first-round PCR consisted of 10 cycles of 94 °C for 35 s, 59 °C for 35 s (decreasing by 2 °C every other cycle), 72 °C for 70 s; and 30 cycles of 94 °C for 35 s, 56 °C for 35 s, 72 °C for 70 s. The second-round PCR (conducted in the same tube) consisted of 35 cycles of 94 °C for 25 s, 56 °C for 25 s, and 72 °C for 50 s. PCR products were purified using a QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany). Sequencing was performed using an ABI 3730xl DNA Analyzers (Applied Biosystems, Foster City, CA). Analysis and assembly of sequencing data were performed with the Vector NTI Suite software package (Informax, Frederick, MD, USA).

Table 2
Baseline characteristics of LAM-resistant patients with CHB before receiving different rescue strategies.

Variables	Switching to ADV monotherapy	Switching to ETV monotherapy	Adding on ADV	Switching to ADV + ETV	P value
Sex (male/female)	185/22	43/7	65/7	6/3	0.183
Age (years)					
Median (quartile range)	43 (14)	43 (12)	39 (14.5)	45 (11)	0.310
Cirrhosis/no cirrhosis	36/171	8/42	20/52	2/7	0.233
HBeAg+/HBeAg-	187/20	42/8	61/11	8/1	0.365
Genotype (C/B)	182/25	40/10	57/15	7/2	0.150
HBV DNA (IU/mL)					
Median (quartile range)	890,000 (903,200)	772,900 (6,758,300)	830,000 (5,418,469)	899,600 (5,176,820)	0.230
ALT (U/L)					
Median (quartile range)	59 (86)	53 (68)	62 (92)	60 (82)	0.260
LAM-resistant mutations	68 (32.85%)	17 (34.00%)	29 (40.28%)	3 (33.33%)	
rtM204I/V					
rtM204I/V + (rtL80I/M and/or rtL180 M and/or rtV173L)	139 (67.15%)	33 (66.00%)	43 (59.72%)	6 (66.67%)	

LAM, lamivudine; ADV, adefovir; ETV, entecavir; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase.

2.4. HBV genotype analysis

The genotyping was based on S-gene sequences encompassing the RT domain of HBV, which was amplified as the above. HBV genotype was determined by molecular evolutionary analysis of the viral sequences using the MEGA4 software. Phylogenetic trees were constructed using neighbor-joining analysis with bootstrap test confirmation performed on 1000 resamplings. Standard reference sequences were acquired from the online hepatitis virus database (<http://www.ncbi.nlm.nih.gov/projects/genotyping/formpage.cgi>) as previously reported (Fang et al., 2009).

2.5. Statistical analysis

Data analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as median (quartile range). Categorical data were expressed as the number of subjects. Group comparisons were performed using the Kruskal–Wallis test for continuous variables, and the Fisher's exact test for categorical variables. A probability value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

338 patients developing rtM204V/I and/or rtL80I/M, rtL180M, rtV173L mutations (Patients developing rt181 site mutation were not included) were finally included, and four rescue strategies were documented to treat patients with LAM resistance. Of these 338 patients, 207 switched to ADV monotherapy, accounting for 61.24%; 50 switched to ETV monotherapy, accounting for 14.79%; 72 added on ADV, accounting for 21.30%; 9 switched to combination of ADV and ETV, accounting for 2.66%. The baseline characteristics of these patients were summarized in Table 2. There were no statistically significant differences in sex composition, median age, cirrhosis composition, HBeAg status, genotypes, median serum HBV DNA level or median ALT level among the four groups. The median duration time after initiation of the above four rescue therapies was respectively 18 months, 17 months, 23 months and 18 months, and no statistical significance existed among the four groups ($P = 0.070$) (Fig. 1).

3.2. Drug resistance analysis

During the rescue treatment period, virological breakthrough and genotypic resistance were detected in 63 patients, including 49 of 207 patients (23.67%) who switched to ADV monotherapy,

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