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Dynamics of hepatitis B virus resistance substitutions correlates with virological response in lamivudine-refractory patients with entecavir rescue monotherapy

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ABSTRACT

Entecavir (ETV) demonstrates potent antiviral effects against lamivudine (LMV)-resistant hepatitis B virus (HBV). This study was designed to investigate the impact of LMV resistance mutations on the outcome of ETV rescue therapy in LMV-refractory patients. Twenty-six chronic hepatitis B patients who received ETV monotherapy for LMV resistance were enrolled. Dynamics of HBV DNA levels were monitored before and during ETV rescue therapy. Mutations in the HBV reverse transcriptase were examined by sequencing. LMV-resistant mutations (rtL180M and/or rtM204VI) were detected in 9 patients before ETV treatment and not in another 5 patients before and after the treatment. ETV therapy resulted in a greater reduction in the HBV DNA load in the patients with out LMV-associated mutations before treatment than in those with. Six patients with 100% LMV-resistant HBV variants at week 12 posttreatment had significantly ($P < 0.01$) greater HBV DNA levels at the end of follow-up than the other patients studied. A comparable outcome was achieved between the patients with or without emergence of LMV-resistant mutations during the ETV treatment. In conclusion, patients without 100% LMV-resistant HBV mutants at week 12 and those without LMV-resistant mutations before treatment show a better response to ETV rescue therapy than the corresponding others. Therefore, individual treatment optimization is of significance in improving the efficacy of antiviral therapy for patients with chronic HBV infection.

1. Introduction

Hepatitis B virus (HBV) is a noncytopathic, enveloped DNA virus that replicates primarily in hepatocytes. Chronic HBV infection is one of the leading causes of mortality worldwide, with an estimated one million deaths every year (Sherman et al., 2008; Foster et al., 2003; Dryden et al., 2006). Patients with recurrent HBV infection are at a high risk of developing progressive liver diseases including fibrosis, cirrhosis, hepatocellular carcinoma, and even hepatic failure (Colonno et al., 2006). Therefore, effective antiviral therapy is necessary in HBV-infected patients, with the primary goal of achieving sustained virological suppression.

Lamivudine (LMV) is the first oral nucleoside analogue approved by the Food and Drug Administration to treat HBV infection. LMV exerts its anti-polymerase activity by inhibiting elongation of the HBV DNA minus strand and acting as a chain terminator through incorporation into the nascent DNA strand (Pallier et al., 2006; Sherman et al., 2006). Despite an initial reduction in HBV viral load, long-term therapy with LMV may lead to the emergence of drug-resistance mutations, thus limiting the therapeutic efficacy.

Entecavir (ETV) is a novel nucleoside analogue and displays potent activity against wild-type and LMV-resistant HBV strains. A direct comparative study shows that ETV therapy results in a greater reduction in the HBV DNA level than LMV and is associated with a high genetic barrier to resistance (Tenney et al., 2007). As a new hope for the treatment of chronic hepatitis B patients, ETV has been shown to be safe and effective for the treatment of LMV-refractory patients with chronic HBV infection (Sherman et al., 2008). In this study, we investigated the dynamics of HBV quasispecies in LMV-refractory patients with chronic hepatitis B during ETV rescue monotherapy and its correlation with virological response.

2. Materials and methods

2.1. Patients

We studied 26 patients with chronic hepatitis B who had developed virological resistance to LMV and were positive for hepatitis

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Table 1
Virological and biochemical responses at indicated time points in 26 patients with entecavir rescue therapy.

Patients	Baseline			Week 24			Week 48			Week 96			Week 168		
	ALT	AST	HBV DNA (log_{10} copies/ml)	ALT	AST	HBV DNA (log_{10} copies/ml)	ALT	AST	HBV DNA (log_{10} copies/ml)	ALT	AST	HBV DNA (log_{10} copies/ml)	ALT	AST	HBV DNA (log_{10} copies/ml)
1	64	37	8.7	150	66	4.3	19	22	2.5	42	27	2.5	34	22	2.5
2	237	90	8.9	41	27	4.5	79	38	4.3	48	27	4.0	27	23	2.5
3	246	119	9.1	31	34	2.3	23	35	2.5	21	25	2.5	61	49	2.5
4	104	49	7.4	50	30	3.6	145	27	3.3	32	22	3.2	50	31	5.5
5	24	26	11.2	31	28	4.3	21	23	3.6	20	24	2.5	13	18	2.5
6	44	26	9.0	71	38	5.5	12	19	7.4	14	19	7.2	10	17	3.6
7	25	25	9.0	19	28	3.8	19	24	3.5	18	24	2.5	20	23	2.5
8	19	16	9.1	17	14	6.9	27	19	6.3	16	13	6.4	49	22	5.8
9	37	26	8.8	21	23	7.2	18	20	6.9	20	18	7.2	33	12	9.1
10	41	31	9.2	41	30	4.9	28	25	4.2	51	34	2.6	30	29	2.5
11	46	30	9.1	40	31	3.7	31	24	3.5	47	27	2.5	22	20	2.5
12	42	44	9.2	27	32	5.1	16	24	4.4	17	24	3.9	11	18	3.5
13	164	91	8.6	21	19	2.3	11	16	2.5	13	17	2.5	15	15	3.2
14	56	55	9.0	35	29	5.1	21	20	5.1	30	25	4.6	20	18	3.7
15	27	24	9.0	15	22	4.2	16	23	3.9	19	22	2.5	15	13	2.5
16	125	87	10.0	26	24	3.5	56	43	3.5	39	30	2.3	25	26	8.2
17	26	33	9.1	20	29	4.2	18	23	4.3	22	24	3.9	38	20	3.2
18	41	46	9.0	58	40	3.9	52	36	4.0	48	38	2.8	32	26	2.5
19	32	25	9.0	58	41	4.8	65	40	4.6	63	38	4.5	9	14	2.5
20	15	18	9.7	22	23	4.2	12	18	4.4	19	19	4.2	11	12	2.7
21	18	21	7.7	14	19	6.0	18	22	5.7	23	23	4.3	14	15	7.2
22	64	31	8.9	64	36	5.7	46	29	5.9	42	22	5.8	57	48	6.2
23	33	25	9.2	24	25	5.2	11	21	4.9	8	15	4.6	54	14	4.9
24	99	71	9.7	15	25	2.6	12	20	2.5	12	19	2.5	100	16	2.5
25	33	100	9.9	58	56	4.7	62	68	3.8	43	42	3.8	37	34	2.5
26	43	33	8.7	36	32	5.2	86	53	4.8	63	37	2.5	29	27	2.5

ALT, alanine transaminase, IU/L; AST, aspartate aminotransferase, IU/L; HBV, hepatitis B virus.