

Efficacy of 3 years of adefovir monotherapy in chronic hepatitis B patients with lamivudine resistance

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Abstract

AIM: To study the effect of rescue monotherapy with adefovir (ADV) in patients with chronic hepatitis B (CHB) who developed drug resistance to lamivudine (LAM).

METHODS: A total of 76 treated CHB patients with resistance to LAM were enrolled in the present study. The patients' baseline characteristics, such as age, gender, blood tests and hepatitis B virus (HBV) DNA were collected; therapy duration and the response of each patient were also recorded. ADV monotherapy was set as the observation group A. Twenty-four patients with LAM resistance, who were set as group B, accepted combined therapy with LAM + ADV. Patients were followed up at 0, 12, 24, 52, 104 and 156 wk. Hepatitis B surface antigen status, hepatitis B e antigen (HBeAg)/anti-HBe status, HBV DNA level and biochemical indexes were monitored. Sequencer of HBV polymerase gene was performed on the ABI 3730

automated sequencer. If no desired effects had been achieved during the course of treatment, patients' choices were also taken into account. The control group was tested at the same time.

RESULTS: In the two groups, 27 cases developed viral breakthrough after LAM treatment response. The remaining 49 cases underwent biochemical rebound accompanied by rtM204I/V or rL180M mutation. In group A, 52 cases finished 156 wk of ADV monotherapy; of whom, 36 cases were HBeAg positive and 16 HBeAg negative. In patients whose baseline HBV DNAs were 10^3 - 10^5 copies/mL, 88.8% of patients' HBV DNAs were lower than the lower test limit (10^3 copies/mL) after 12 to 156 wk of ADV treatment. In patients whose baseline HBV DNAs were $\geq 10^6$ copies/mL, 41.1%-47.0% of patients' HBV DNAs were lower than the lower test limit after the same course of ADV therapy (χ^2 were 4.35-5.4, 41.1%-47.0% vs 88.8% group 10^3 - 10^5 copies/mL, $P < 0.01$). In group A, seroconversion of HBeAg developed in 8 of 36 cases (22.2%). In group B, 24 cases finished 156 wk of LAM + ADV; of whom, 17 cases were HBeAg positive and 7 HBeAg negative. In patients whose baseline HBV DNAs were 10^3 - 10^5 copies/mL, 81.8% of patients' HBV DNAs were lower than the lower test limit (10^3 copies/mL) after 12 to 156 wk of treatment. In the patients whose baseline HBV DNAs were $\geq 10^6$ copies/mL, 46.1%-53.8% of patients' HBV DNAs were lower than the lower test limit after the same course of LAM + ADV therapy (χ^2 were 4.1-5.0, 46.1%-53.8% vs 81.8% group 10^3 - 10^5 copies/mL, $P < 0.05$ -0.01). In group B, 4 of 17 cases (23.5%) developed seroconversion of HBeAg. Treatment outcomes in groups A and B were comparable.

CONCLUSION: In both group A and B, the ratios of virological response have similar efficacy in patients with lower baseline HBV DNAs.

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Key words: Adefovir; Lamivudine; Drug resistance; Chronic hepatitis B; Antiviral therapy; Monotherapy

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INTRODUCTION

The main treatment for chronic hepatitis B (CHB) is antiviral therapy. Nucleoside analogues are one of the major choices. However, drug resistance hinders nucleoside analogues from a wide application, especially in cases of long-term oral administration. When multiple drugs are used, the occurrence of single or multiple drug resistance is an issue that cannot be neglected. Considering the need for nucleoside administration in the long run, an appropriate strategy is necessary so that multiple drug resistance can be avoided.

Lamivudine (LAM) resistance is fairly common in clinical practice. The present study was performed in order to evaluate the efficacy of single rescue therapy with adefovir (ADV). We hope to determine (1) the feasibility of single agent salvage therapy with ADV in LAM resistant cases; and (2) whether a predicted efficacy can be derived from the baseline hepatitis B virus (HBV) DNA load.

MATERIALS AND METHODS

Patients

During the period between April 2006 and March 2007, there were 85 cases of patients who failed the initial LAM treatment in our hospital. Among those cases, 27 cases developed viral breakthrough after LAM treatment response. Viral breakthrough was defined as serum HBV DNAs rebound greater than 10^2 copies/mL. The remaining 49 cases underwent biochemical rebound accompanied by rtM204I/V or rtL184M mutation. In group A, 52 cases were employed and oral ADV in 10 mg/d was given for 8 wk before the cessation of LAM. In group B (24 cases), ADV of 10 mg/d and LAM of 100 mg/d were administered. Diamine glycyrrhizin or silymarin was used for patients with elevated alanine aminotransferase (ALT). Patients were excluded if they had the following: interferon administration in the last 6 mo; combined infection of HCV or HDV; autoimmune hepatitis; elevated confirmed liver cancer or suspected liver cancer; decompensated liver disease; and a history of alcohol abuse, pregnancy or breast-feeding. The diagnosis was made according to the guidelines^[1]. There was no history of immunomodulatory agent administration in the last 6

Table 1 Baseline demographic and virological data of the study population

Factor	A group n (range)	B group n (range)
Sex (M:F)	38:14	18:6
Age (yr)	27.6 (19-60)	25.7 (18-59)
ALT (U/L)	165 (44-1000)	230 (110-640)
HBeAg positive/HBeAg negative	36:16	17:7
HBV DNA (log copies/mL)	7.35 (3.00-9.0)	7.5 (3.0-9.0)
LAM-induced mutation of HBV DNA and rebound	40:12	20:4

Continuous variables were expressed as median (range). M: Male; F: Female; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; LAM: Lamivudine.

mo. All patients gave informed consent before treatment. Finally, 52 patients were enrolled in ADV single drug and 24 patients were enrolled ADV plus LAM in this prospective research. In patients with HBeAg-positive CHB, combined response was defined as ALT levels returning to normal, accompanied by undetectable HBV DNA and HBeAg seroconversion; partial response was defined as ALT levels returning to normal, HBV DNA $< 10^3$ copies/mL with no seroconversion.

Monitoring of patients

Patients were followed up at 12, 24, 52, 104 and 156 wk. Hepatitis B surface antigen status, hepatitis B e antigen (HBeAg)/anti-HBe status, HBV DNA level and biochemical indexes were monitored. If no desired effects had been achieved during the course of treatment, patients' choices were also taken into account. Group B was tested at the same time.

Sequencing of HBV polymerase gene and assay of HBV DNA

Sera from patients on presentation were taken for the following tests: (1) sequencing of HBV polymerase gene, which was performed on the ABI 3730 automated sequencer; and (2) assay of HBV DNAs, which was determined by quantitative fluorescence polymerase chain reaction (PCR) on the ABI 7000 (Applied Biosystems) with a lower limit of detection of 1000 copies/mL. HBV DNAs levels lower than the detection limit were regarded as negative for statistical calculations.

RESULTS

Demographics

A total of 76 CHB patients were enrolled. The baseline demographics, liver function tests, liver biochemistry, HBV Gene sequencing determination data and HBV DNAs levels are listed in Table 1.

Baseline characteristics and treatment outcomes

At 12, 24, 52, 104 and 156 wk, there was no statistical difference in the number of patients who achieved virological response (VR, defined as HBV DNA $<$ lower

Table 2 Control of the therapeutic effect in the two groups

Group	Baseline (copies/mL)	n	12 wk		24 wk		52 wk		104 wk		156 wk	
			VR ¹	BR ²	VR ¹	BR ²	VR ¹	BR ²	VR ¹	BR ²	VR ¹	BR ²
A	10 ³ -10 ⁵	18	16 (88.8) ¹	16 (88.8)	16 (88.8) ¹	16 (88.8)	16 (88.8) ³	16 (88.8)	16 (88.8) ¹	16 (88.8)	16 (88.8) ¹	16 (88.8)
A	≥ 10 ⁶	34	14 (41.1)	24 (70.5)	15 (44.1)	30 (88.2)	16 (47.0)	22 (64.7)	16 (47.0)	26 (76.4)	16 (47.0)	18 (52.9)
B	10 ³ -10 ⁵	11	9 (81.8) ⁴	9 (81.8)	9 (81.8) ⁴	10 (90.9)	9 (81.8) ⁴	10 (90.9)	8 (72.7)	9 (81.8)	9 (81.8) ⁴	9 (81.8)
B	≥ 10 ⁶	13	6 (46.1)	10 (76.9)	6 (46.1)	10 (76.9)	6 (46.1)	9 (69.2)	7 (53.8)	9 (69.2)	6 (46.1)	9 (69.2)
A	HBeAg positive	36	18 (50.0)	26 (72.2)	20 (55.5)	30 (83.3)	20 (55.5)	26 (72.2)	22 (61.1)	26 (72.2)	20 (55.5)	22 (61.1)
A	HBeAg negative	16	12 (75.0)	14 (87.5)	14 (87.5)	16 (100.0)	12 (75.0)	12 (75.0)	14 (87.5)	16 (100.0)	12 (75.0)	6 (75.0)
B	HBeAg positive	17	8 (47.8)	12 (70.5)	9 (52.9)	15 (88.2)	9 (52.9)	15 (88.2)	9 (52.9)	13 (76.4)	10 (58.8)	11 (64.7)
B	HBeAg negative	7	5 (71.4)	6 (85.7)	5 (71.4)	6 (85.7)	6 (85.7)	6 (85.7)	5 (71.4)	6 (85.7)	5 (71.4)	6 (85.7)
A	ALT < 2 × ULN	20	17 (85.0)	18 (90.0)	16 (80.0)	18 (90.0)	14 (70.0)	14 (70.0)	14 (70.0)	18 (90.0)	14 (70.0)	14 (70.0)
A	ALT > 2 × ULN	32	18 (56.2)	22 (68.7)	18 (56.2)	28 (87.5)	18 (56.2)	26 (81.2)	22 (68.7)	24 (75.0)	18 (56.25)	20 (62.5)
B	ALT < 2 × ULN	10	8 (80.00)	9 (90.0)	8 (80.0)	10 (100.0)	8 (80.0)	10 (100.0)	8 (80.0)	10 (100.0)	8 (80.0)	9 (90.0)
B	ALT > 2 × ULN	14	8 (57.1)	10 (71.4)	8 (57.1)	12 (85.7)	10 (71.4)	12 (85.7)	10 (71.4)	12 (85.7)	10 (71.4)	12 (85.7)

Group A: Treated with adefovir; Group B: Treated with adefovir and lamivudine; ¹VR: Defined as HBV DNA < lower detection limit; ²BR: Defined as ALT < lower detection limit; ³P < 0.01 ($\chi^2 = 4.35-5.4$) vs group A with baseline HBV DNA ≥ 10⁶ copies/mL; ⁴P < 0.05 ($\chi^2 = 4.1-5.0$) vs group B with baseline HBV DNA ≥ 10⁶ copies/mL. VR: Virological response; BR: Biochemical response; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase.

Table 3 Response to adefovir salvage therapy n (%)

Project	HBV DNA (copies/mL)			HBeAg positive		rtA181V/S variation
	10 ³	10 ³ -10 ⁶	≥ 10 ⁷	HBeAg seroconversion	HBeAg elimination	Change drug
Baseline level	A	12 (23.0)	22 (42.43)	18 (34.6)	36	
	B	5 (20.8)	11 (45.8)	8 (33.3)	17	
12 wk	A	30 (57.7) ¹	18 (34.6)	4 (7.6) ²	0 (0)	2 (5.5)
	B	14 (58.3) ⁴	8 (33.3)	2 (8.3) ⁵	1 (5.8)	1 (5.8)
24 wk	A	32 (61.5) ⁴	20 (38.4)	0 (0) ³	4 (11.1)	2 (5.5)
	B	15 (62.5) ⁴	8 (33.3)	1 (4.1) ⁵	2 (11.7)	2 (11.7)
52 wk	A	34 (65.4) ¹	18 (34.6)	0 (0) ³	4 (11.1)	2 (5.5)
	B	16 (66.6) ⁴	8 (33.3)	0 (0) ³	4 (23.5)	2 (11.7)
104 wk	A	36 (69.2) ¹	16 (30.7)	0 (0) ³	8 (22.2)	4 (11.1)
	B	16 (66.6) ⁴	8 (33.3)	0 (0) ³	4 (23.5)	2 (11.7)
156 wk	A	34 (65.4) ¹	16 (30.7)	2 (3.8) ³	8 (22.2)	6 (16.6)
	B	15 (62.5) ⁴	8 (33.3)	1 (4.1) ⁵	4 (23.5)	2 (11.7)

Group A: Treated with adefovir; Group B: Treated with adefovir and lamivudine; ¹P < 0.001 ($\chi^2 = 6.4-11.0$) vs group A baseline HBV DNA 10³ copies/mL; ²P < 0.05 ($\chi^2 = 4.7$); ³P < 0.01 ($\chi^2 = 7.9-10.8$) vs group A baseline HBV DNA 10⁷ copies/mL; ⁴P < 0.001 ($\chi^2 = 5.9-11.7$) vs group B baseline HBV DNA 10³ copies/mL; ⁵P < 0.01 ($\chi^2 = 7.7-11.0$) vs group B baseline HBV DNA 10⁶ copies/mL. HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

detection limit) or biochemical response (defined as ALT < lower detection limit) between the two groups with a baseline of HBeAg positive and HBeAg-negative. More than that, there was also no statistical difference between the two groups with a baseline ALT < 2 × upper limit of normal (ULN) and ALT > 2 × ULN. However, patients with a lower baseline HBV DNA level tended to have a higher VR ratio. Baseline HBV DNAs, HBeAg status, ALT and their relationship to treatment outcomes of each group are shown in Table 2.

HBeAg seroconversion state in treatment course with ADV monotherapy

As shown in Table 3, after 12 wk of treatment, HBeAg seroconversion was 0/36 cases in group A. At 24 and 52 wk, it was 4/36 cases (11.1%). After 104 and 156 wk of treatment, the HBeAg seroconversion ratio rose in 8/36

cases (22.2%). After 12 to 52 wk of treatment, HBeAg turned negative in 2/36 cases (5.5%). After 156 wk of treatment, HBeAg turned negative in 6/36 cases (16.6%). The ratio of HBV DNAs lower than 10³ copies/mL gradually increased with the treatment course when compared with the baseline (χ^2 were 6.4-11.0, 23.05% vs 65.4%, P < 0.01). After treatment, the ratio of HBV DNAs > 10⁷ copies/mL decreased gradually with the treatment course (χ^2 were 4.07-10.8, 3.8% vs 34.6%, P < 0.05-0.01). No significant difference was observed in either group.

The handling of poor effect and viral rebound

During treatment, 10 cases underwent poor response or viral rebound. The rtA181V/I/S loci variation was detected in 4 cases (7.6%). Entecavir (ETV) was added at 52 and 108 wk. After one year, the 2nd HBV polymerase gene sequencing was performed and rtM204I variation

persisted in 2 cases (2/10). Although ALT turned to normal, HBV DNAs were higher than 10^3 copies/mL in the time course. Six patients shifted to ETV at 24 wk. At 104 wk, 10 patients' ALT turned normal with HBV DNAs $< 10^3$ copies/mL. However, after self-withdrawal at 4-12 wk, ALT became abnormal. In group B, 3 patients (12%) at 104 and 156 wk respectively were detected with rtA181V/I/S and rtM204I, rtL180M sites of variation.

DISCUSSION

In the treatment of chronic hepatitis B, ADV tends to induce mutations of the HBV genome that are different from that of LAM. Thus, ADV may serve as an alternative for the patients with LAM resistance. Due to the earlier entry of LAM into China's market, ADV used to act as a salvage therapy in patients who could not gain a satisfying response or have resistance to LAM. Several reports have indicated that combined use of ADV and LAM surpasses single salvage treatment with ADV^[2-6]. However, the enrolled patients were limited. More than that, expenditure and multi-drug resistance are worthy of care^[7,8]. Thereupon, we executed single salvage treatment of ADV in 2006 in patients who developed resistance to LAM. Similarly to the observation of Shin *et al.*^[9], Lee *et al.*^[10] and Kim *et al.*^[11] patients who have a lower viral load tended to have a higher response ratio to ADV monotherapy. We also observed that patients who have a higher viral load usually have a poor response, which agreed with Idilman *et al.*^[12], Chen *et al.*^[13] and Aizawa *et al.*^[14]. Unauthorized withdrawal of drugs would lead to the rebound of HBV DNA. In the cases where HBV DNAs cannot return to normal, the ratio of ALT normalization was also low. After 156 wk of treatment, the ratio of HBeAg seroconversion was 22.2% (8/36 cases), which was similar to both Aizawa *et al.*^[15], Ryu *et al.*^[16] and Heo *et al.*^[17] of single rescue therapy of ADV in patients who developed drug resistance to LAM and the ratio of HBeAg seroconversion in patients who accepted single ADV treatment for the first time. After ADV salvage therapy, the proportion of patients whose HBV DNAs were lower than 10^3 copies/mL increased gradually with time compared with the baseline. The number of patients whose HBV DNAs were higher than 10^7 copies/mL decreased gradually with time compared with the baseline (Table 2). The overall decline of HBV DNA load was similar to that in the initial treatment with ADV^[18]. Variation of rtA181V/I/S loci was detected in 4 cases (7.6%) after 104 wk of treatment. Among them, 2 cases (3.8%) remained with rtM204I loci variation after 52 wk of ADV treatment. Meanwhile, the cases remained in a state of low HBV DNAs load and ALT were stable. Mutation rate was similar to that in the report of initial treatment of ADV. No multiple resistance sites were screened out. In group A, HBV DNA was slightly higher than group B. However, it was more difficult to deal with multiple points of resistance.

Our results showed that single salvage therapy of

ADV has a certain effect on patients who developed resistance to LAM. We think it is suitable to initiate ADV salvage therapy in patients whose HBV DNA is in 10^3 - 10^5 copies/mL, although timely monitoring on HBV DNA load is needed. It is sagacious to adopt combination therapy if no satisfying effect is achieved. Chen *et al.*^[19] has also observed that no additional benefit may be gained in initiating combination therapy at the very beginning^[20,21]. HBV DNA load at 24 wk or 12 mo may serve as a predictor of ADV resistance^[22-25]. Single salvage therapy with ADV is conducive to reducing non-individualized combination therapy, the potential hazards of multiple drug resistance, the financial burden and mental stress of patients due to long-term additional medication and to enhance compliance. ADV rescue treatment cannot gain a satisfying effect in LAM resistant cases which may stem from the limitation of ADV in patients with high HBV DNA loads. No significant difference was observed in the two groups. Timely detection of HBV DNA load, virological breakthrough and genome variation are necessary for the achievement of a preferable response. In the patients who do not have desired outcome, combined therapy may be a suitable strategy.

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COMMENTS

Background

The greatest challenge in the treatment of hepatitis B with a nucleoside was drug resistance after long-term treatment. At the same time, with the multi-drug combination, resistance to the multi-drug is also a matter of time. Due to the earlier entry of resistance to lamivudine (LAM) into China's market, adefovir (ADV) is used as a salvage therapy in patients who cannot gain a satisfying response or have resistance to LAM. Several reports have indicated that the combined use of ADV and LAM surpasses single salvage treatment with ADV. However, hepatitis B virus (HBV) DNA may have a significant influence on the antiviral effect of ADV. The present research aims at evaluating the effect of ADV monotherapy on LAM resistant patients with diverse levels of HBV DNA.

Research frontiers

How to control and reduce the occurrence of nucleoside resistance is a current difficulty and hot issue. Particularly, it is great challenge when multiple drug and long term administration are needed. To date, there is no satisfying solution for this issue.

Innovations and breakthroughs

Although there is debate on whether ADV or ADV plus LAM should be used for the rescue treatment on LAM resistance, HBV DNA level may have a significant effect on the efficacy of salvage therapy. Sagacious and individualized choice should be made for patients with different HBV DNA levels.

Applications

Although multicenter and randomized observations are needed, the present research may shed light on the strategy of rescue therapy on LAM resistance.

Terminology

Salvage therapy: A therapeutic approach, involving chemotherapy, radiation therapy or surgery, after initial regimens have failed to lead to improvement in a patient's condition. Salvage therapy is most often used for neoplastic diseases; Drug resistance: Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug.

Peer review

The authors' aim is important, although it is difficult to understand how the

authors selected observation and control groups among chronic hepatitis B patients. The authors prospectively evaluated the effectiveness of ADV vs ADV + LAM treatment in patients with lamivudine resistance. They concluded that combination therapy should be used in patients with high DNA levels. This conclusion has practical implications.

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