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BRIEF ARTICLE

Virological response to adefovir monotherapy and the risk of adefovir resistance

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Abstract

AIM: To evaluate virological response to adefovir (ADV) monotherapy and emergence of ADV-resistant mutations in lamivudine (LAM)-resistant chronic hepatitis B patients.

METHODS: Seventy-seven patients with documented LAM resistance who were treated with 10 mg/d ADV for > 96 wk were analyzed for ADV resistance.

RESULTS: At week 48 and 96, eight (10%) and 14 (18%) of 77 LAM-resistant patients developed the ADV-resistant strain (rtA181V/T and/or rtN236T mutations), respectively. Hepatitis B virus (HBV) DNA levels during therapy were significantly higher in patients who developed ADV resistance than in those who did not. Incidence of ADV resistance at week 96 was 11%, 8% and 6% among patients with complete virological response (HBV DNA level < 60 IU/mL); 0%, 5% and 19% among patients with partial virological response (HBV DNA level ⩾ 60 to 2000 IU/mL); and 32%, 34% and 33% among patients with inadequate virological response (HBV DNA levels > 2000 IU/mL) at week 12, week 24 and week 48, respectively. HBV DNA levels > 2000 IU/mL at week 24 showed best performance characteristics in predicting ADV resistance.

CONCLUSION: Development of ADV resistance mutations was associated with HBV DNA levels, which could identify patients with LAM resistance who are likely to respond to ADV monotherapy.

Key words: Hepatitis B virus; Viral DNA; Adefovir; Lamivudine; Drug resistance

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INTRODUCTION

Lamivudine (LAM) has been the most popular antiviral agent for the treatment of chronic hepatitis B for many years, but its efficacy is hampered by the high incidence of drug resistance[1]. Adefovir dipivoxil (ADV) is a nucleotide analog that exhibits activity against wild-type and LAM-resistant hepatitis B virus (HBV)[2-4]. Early

studies have demonstrated potent viral suppression of LAM-resistant HBV by either switching to or adding ADV to LAM[5]. However, ADV-resistant strains have been reported after either switching to or adding ADV in patients with LAM resistance, and several recent clinical studies have found that combined LAM with ADV is associated with improvements in virological response and lower rates of ADV resistance than sequential ADV monotherapy[6-8]. Thus, recent guidelines suggest adding ADV to LAM as a better approach than sequential monotherapy for patients with LAM resistance[9-12].

Although ADV add-on therapy represents a new paradigm that is highly effective at restoring viral suppression and preventing the emergence of resistance in patients with LAM resistance[13], the higher cost of add-on therapy may allow ADV monotherapy to retain its role in selected patients, particularly in developing countries[14]. In clinical practice, some patients with LAM resistance do respond to ADV monotherapy[15]. Identification of patients who may be sufficiently treated with ADV monotherapy alone may reduce medical costs in areas where resources are limited.

HBV DNA levels on treatment may help select patients who are likely to respond to ADV monotherapy. Maintenance of undetectable HBV DNA levels during treatment with nucleoside/nucleotide analogs has been suggested as a desirable endpoint[10]. Recently proposed "on-treatment strategy" for patients receiving oral nucleoside/nucleotide therapy is also based on HBV DNA levels[16]. On-treatment monitoring strategies are based on the nature of virological response during treatment, and HBV DNA levels during treatment may be a valuable predictor of treatment response to ADV monotherapy.

The aim of this study was to establish whether HBV DNA levels during treatment are associated with the emergence of genotypic ADV resistance. We studied HBV DNA levels at weeks 12, 24 and 48 after the start of ADV monotherapy among LAM-resistant patients who had received ADV monotherapy for > 96 wk and assessed genotypic resistance to ADV at weeks 48 and 96.

MATERIALS AND METHODS

Patients

Data were collected retrospectively from 85 LAM-resistant chronic hepatitis B patients who started ADV monotherapy between March 2004 and May 2006, and maintained ADV monotherapy for at least 96 wk at the Samsung Medical Center, Seoul, Korea. All 85 patients were treated with LAM for chronic HBV infection and experienced virological breakthrough (VB), which was defined as an increase in the level of HBV DNA of at least 1 $\log_{10}$ IU/mL from the lowest point during treatment. Serum samples were collected every 3 mo during treatment and kept at -80℃ until mutation analyses were performed. Eight patients were excluded from analyses for the following reasons: (1) serum samples were not available for six patients; and (2) an ADV-resistant strain (rtA181V/T) was present at baseline in two patients. Finally, a total of 77 patients were included in this study. This study was approved by the Institutional Review Board at Samsung Medical Center.

Blood tests

Routine biochemical tests were performed by standard procedures every 12 wk during therapy. Hepatitis B surface antigen, hepatitis B e antigen (HBeAg), and hepatitis B e antibody were tested by electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Indianapolis, IN, USA). LAM resistance was tested with direct sequencing (ABI 3130 Genetic Analyzer; Applied Biosystems, Foster City, CA, United States).

HBV DNA assay

HBV DNA was quantified using the COBAS TaqMan HBV test (detection limit of 12 IU/mL, Roche Molecular Systems, Branchburg, NJ, USA) at the onset of ADV treatment (baseline), and at weeks 12, 24 and 48 using stored serum samples. Virological response was defined as complete virological response (CVR, HBV DNA level < 60 IU/mL); partial virological response (PVR, HBV DNA levels ⩾ 60 to 2000 IU/mL); and inadequate virological response (IVR, HBV DNA levels > 2000 IU/mL)[13]. VB was defined as an increase in the level of HBV DNA of at least 1 $\log_{10}$ IU/mL from the lowest point during treatment[13].

Detection of ADV resistance

Genotype resistance to ADV was determined at baseline and at weeks 48 and 96 by direct sequencing after amplification of polymerase chain reaction (PCR) products. To detect mutations, PCR amplification was performed using the following primers: external primers were RTF (5'-tat gtt gcc cgt ttg tcc tc-3', position 460-479) and RTR (5'-tga cat act ttc caa tca ata gg-3', position 970-992); internal primers were RTNF (5'-aaa acc ttc gga cgg aaa ct-3', position 574-593) and RTNR (5'-tgc ggt aaa gta ccc caa ct-3', position 895-914). The PCR-amplified DNA was purified by using a QIAquick PCR purification kit (QIAGEN, Hilden, Germany). Purified DNA was treated with an ABI Prism BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems). The primers used for direct sequencing were RTNS and RTNR. DNA sequencing was performed in both directions by an Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems). In this study, ADV resistance was defined as the presence of mutations that confer resistance to ADV, which were rtN236T and/or rtA181V/T[17,18].

Statistical analysis

Differences between patient groups were tested using *t* tests or Mann-Whitney *U* tests, as appropriate, for numeric variables, and χ^2 tests or Fisher's exact tests, as appropriate, for categorical variables. For statistical analysis, HBV DNA levels < 12 IU/mL were considered to be 12 IU/mL. Sensitivity, specificity, positive predictive value, and negative predictive value of HBV DNA levels

Table 1 Baseline characteristics of patients

Variables	
No. of patients	77
Age (yr, mean ± SD)	49.3 ± 11.7
Female: Male (*n*, % male)	18: 59 (77%)
HBeAg positive (*n*, % positive)	21: 56 (73%)
ALT (U/L, median, range)	119 (25–926)
AST (U/L, median, range)	77 (30–483)
Albumin (g/dL, median, range)	4.0 (2.6–4.6)
Total bilirubin (mg/dL, median, range)	1.0 (0.3–4.0)
Prothrombin time (INR, median, range)	1.1 (0.9–1.7)
Baseline creatinine level (mg/dL, mean ± SD)	0.90 ± 0.13
Creatinine level at weeks 96 (mg/dL, mean ± SD)	0.94 ± 0.16
LAM resistance mutation profile (*n*, %)	
rtM204 I ± rtL180M	48 (62%)
rtM204V ± rtL180M	29 (38%)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; LAM: Lamivudine.

Table 2 Patterns of ADV-resistant mutations at weeks 48 and 96 after ADV monotherapy in LAM-resistant patients

Variables	Week 48	Week 96
rtA181T	5	5
rtA181V	2	5
rtA181V + rtN236T	1	2
rtA181T + rtN236T	0	2
Total *n* (%)	8 (10)	14 (18)

LAM: Lamivudine; ADV: Adefovir dipivoxil; rtA181V/T and/or rtN236T: ADV-resistant strain.

Table 3 HBV DNA levels during ADV monotherapy according to emergence of ADV-resistant mutations in LAM-resistant patients

HBV DNA level	ADV resistance at week 96 (*n* = 14)	No ADV resistance at week 96 (*n* = 63)	*P* value
Baseline (log10 IU/mL, mean ± SD)	7.1 ± 0.7	6.8 ± 1.0	0.245
Month 3 (log10 IU/mL, mean ± SD)	4.2 ± 1.6	3.1 ± 1.6	0.027
Month 6 (log10 IU/mL, mean ± SD)	4.1 ± 1.4	2.7 ± 1.6	0.002
Month 12 (log10 IU/mL, mean ± SD)	3.9 ± 1.3	2.4 ± 1.5	0.002

LAM: Lamivudine; ADV: Adefovir dipivoxil; HBV: Hepatitis B virus.

were calculated for the prediction of genotypic resistance to ADV at week 96. Receiver operator curve (ROC) analysis was performed to compare the performance of HBV DNA levels at each time points. Statistical analysis was conducted using PASW Statistics 17.0 (SPSS, Inc., Chicago, IL, United States) and $P < 0.05$ was considered significant.

RESULTS

Genotypic ADV resistance at weeks 48 and 96

Baseline characteristics of enrolled patients are shown in Table 1. At week 48, 8 (10%) of 77 LAM-resistant patients had developed the rtA181V/T and/or rtN236T mutations. At week 96, 14 (18%) of 77 LAM-resistant patients had developed rtA181V/T and/or rtN236T mutations (Table 2).

Table 4 Incidence of ADV resistance according to HBV DNA levels

HBV DNA level	Patient number	ADV resistance at week 48 *n* (%)	ADV resistance at week 96 *n* (%)
Week 12[a]			
< 60 IU/mL	18	2 (11)	2 (11)
≥ 60 to < 2000 IU/mL	21	0 (0)	0 (0)
> 2000 IU/mL	38	6 (16)	12 (32)
Week 24[b]			
< 60 IU/mL	26	2 (8)	2 (8)
≥ 60 to < 2000 IU/mL	19	1 (5)	1 (5)
> 2000 IU/mL	32	5 (16)	11 (34)
Week 48[c]			
< 60 IU/mL	34	2 (6)	2 (6)
≥ 60 to < 2000 IU/mL	16	0 (0)	3 (19)
> 2000 IU/mL	27	6 (22)	9 (33)

[a]*P* value; week 48 = 0.162, week 96 = 0.007. [b]*P* value; week 48 = 0.431, week 96 = 0.008. [c]*P* value; week 48 = 0.036, week 96 = 0.022. ADV: Adefovir dipivoxil; HBV: Hepatitis B virus.

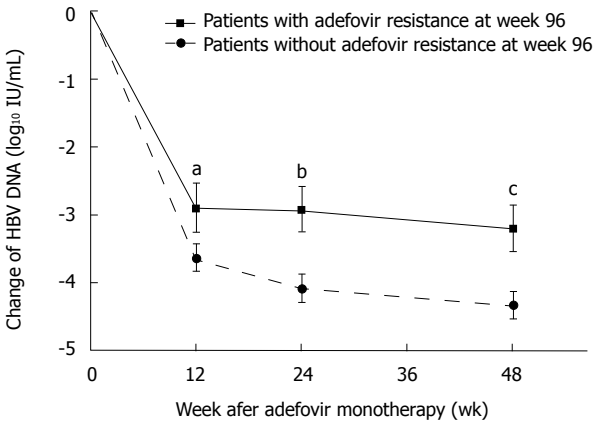

Figure 1 Hepatitis B virus DNA levels after adefovir monotherapy. There were significant differences in the degree of Hepatitis B virus (HBV) DNA reduction between patients who developed adefovir resistance and those who did not (*P* value; [a]week 12 = 0.027, [b]week 24 = 0.002, [c]week 48 = 0.002).

HBV DNA levels on treatment and emergence of ADV resistance

HBV DNA levels during treatment were significantly lower in patients who did not develop ADV resistance than in those who did, while pretreatment HBV DNA levels were not significantly different (Table 3). The degree of reduction of HBV DNA level was also significantly greater among patients who developed ADV resistance (Figure 1). There was a significant difference in the incidence of ADV resistance at week 96 according to HBV DNA levels at week 12 ($P = 0.007$), at week 24 ($P = 0.008$), and at week 48 ($P = 0.022$) (Table 4). Only 8% and 6% of patients with CVR at weeks 24 and 48 developed ADV resistance at week 96, whereas, > 30%

Table 5 Virological response in predicting ADV resistance at week 96

Variables	Adefovir resistance *n* (%)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Positive predictive value (%, 95% CI)	Negative predictive value (%, 95% CI)
HBV DNA level ≥ 60 IU/mL at Week 12 (n = 59)	12 (20)	85 (56–97)	25 (15–38)	20 (11–33)	89 (63-98)
HBV DNA level > 2,000 IU/mL at Week 12 (n = 38)	12 (32)	85 (56–97)	58 (45–70)	31 (18–48)	84 (81–99)
HBV DNA level ≥ 60 IU/mL at Week 24 (n = 51)	12 (24)	85 (56–97)	38 (26-51)	23 (13–38)	92 (73–98)
HBV DNA level > 2000 IU/mL at Week 24 (n = 32)	11 (34)	78 (48–94)	66 (53–77)	34 (19–53)	93 (80–98)
HBV DNA level ≥ 60 IU/mL at Week 48 (n = 43)	12 (28)	85 (56–97)	51 (38–63)	28 (16–44)	72 (56–84)
HBV DNA level > 2000 IU/mL at Week 48 (n = 27)	9 (33)	64 (35–86)	71 (58–81)	33 (17–53)	90 (77–96)

ADV: Adefovir dipivoxil; HBV: Hepatitis B virus.

of patients with IVR at weeks 12, 24 and 48 developed ADV resistance at week 96.

The HBV DNA levels at weeks 12, 24 and 48 were tested for sensitivity, specificity, positive predictive value and negative predictive value for the prediction of ADV resistance at week 96 (Table 5). ROC curve analysis showed that the area under the curve in predicting ADV resistance was lowest at HBV DNA level ≥ 60 IU/mL at week 12 (area = 0.556, P = 0.51) and highest at HBV DNA level > 2000 IU/mL at week 24 (area = 0.726, P = 0.008).

DISCUSSION

In this study, we found that on-treatment serum HBV DNA levels were associated with genotypic ADV resistance. Patients who developed ADV resistance showed higher HBV DNA levels at weeks 12, 24 and 48 after the start of ADV monotherapy. The incidence of ADV resistance was lowest among patients with CVR, and highest among patients with IVR (Table 4). These data suggest that risk of ADV resistance is low among patients who achieve CVR at weeks 12, 24 and 48 after ADV monotherapy, and they may continue ADV monotherapy. IVR at weeks 12, 24 and 48 was associated with development of ADV resistance, and ADV monotherapy should not be continued. Patients with PVR at weeks 12 and 24 showed low incidence of ADV resistance, and may continue ADV monotherapy with careful follow-up, but patients with PVR at weeks 48 may not continue ADV monotherapy because of significant risk of ADV resistance at week 96. The best predictor of ADV resistance was IVR at week 24 (Table 5).

The findings of this study are in line with the recently proposed "on-treatment strategy" for patients receiving oral nucleoside/nucleotide therapy[13]. Keeffe *et al*[13] have suggested that management strategies should be changed for patients with IVR response at week 24. Shin *et al*[19] also have described the importance of HBV DNA levels on treatment among patients with LAM resistance who received ADV monotherapy. They have reported that patients who had HBV DNA levels < 200 IU/mL at week 48 were unlikely to develop VB and genotype mutations. Chen *et al*[20] have reported that ADV resistance was associated with higher HBV DNA levels and lower HBV DNA reduction during the first 6 mo of ADV treatment, compared to patients who did not develop ADV resistance. Gallego *et al*[21] also have shown that initial virological response (reduction ≥ 4 $\log_{10}$ IU/mL) in HBV DNA at 6 mo is an important factor for predicting treatment outcome. These studies, as well as the present study, suggest that HBV DNA level during treatment is a valuable parameter for making early decisions regarding the continuation of ADV monotherapy or switching to another therapy in patients who show LAM resistance[19].

For patients with LAM resistance, adding ADV is a better approach than switching to ADV, as has been demonstrated by several studies[6-12]. However, because of the higher cost of add-on therapy, in areas with limited resources, ADV monotherapy may still be considered. If so, these data suggest that ADV monotherapy may be tried for up to 24 wk, depending on virological response. Patients who show favorable virological response may continue ADV monotherapy.

The cumulative probability of ADV resistance in our series was 10% and 18% at weeks 48 and 96, respectively. However, in this study, only patients who maintained ADV monotherapy for at least 96 wk were enrolled, which indicates that patients who were good responders to ADV were preferentially selected for the study. Thus, the incidence of ADV resistance in this study does not reflect true genotypic resistance rates among LAM-resistant patients who received ADV monotherapy. We included patients only for those who had received at least 96 wk of ADV monotherapy, because the aim of this study was to determine which patients could continue ADV monotherapy.

In conclusion, the results of this study demonstrate the importance of HBV DNA levels during treatment as an indicator of future ADV resistance. The development of ADV-resistant mutations was closely associated with HBV DNA levels during therapy. The risk of developing ADV-resistant mutations in patients who experi-

enced IVR at week 24 was high. These findings suggest that ADV monotherapy is a viable alternative for LAM-resistant patients with good on-treatment virological response, in areas with limited resources.

COMMENTS

Background

A major concern with adefovir (ADV) treatment in lamivudine (LAM)-resistant patients is the selection of ADV-resistant mutations.

Research frontiers

Recent studies suggest that combination therapy with ADV and LAM is better than ADV monotherapy in preventing development of ADV resistance among LAM-experienced patients. However cost is of concern, in areas with limited resources.

Innovations and breakthroughs

Recent reports have highlighted the importance of hepatitis B virus (HBV) DNA levels during antiviral therapy. On-treatment monitoring strategies are based on the nature of virological response during treatment. This study showed that HBV DNA levels during treatment were also useful in predicting ADV resistance in LAM-resistant patients, thus helps to identify patients that might respond to ADV monotherapy.

Applications

This study suggests that ADV monotherapy could be a viable alternative for LAM-resistant patients with good on-treatment virological response to ADV. ADV monotherapy may still be alternative, cost-effective approach especially in areas with limited resources.

Terminology

Genotypic resistance refers to the detection of mutations that have been shown in *in vitro* studies to confer resistance to the drug that is being administered. Antiviral-resistant mutations can be detected at months and sometimes years before biochemical breakthrough. Thus, early detection and intervention can prevent hepatitis flares and hepatic decompensation.

Peer review

This is a retrospective study that evaluated the virological response to ADV monotherapy. This was a good study.

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