The Feasibility of Discontinuing Lamivudine in Lamivudine-Resistant Chronic Hepatitis B Patients on Lamivudine and Adefovir Combination Therapy

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Key Words

Hepatitis B virus · Lamivudine resistance · Adefovir · Combination therapy

Abstract

Objectives: This study investigated the antiviral efficacy of adefovir (ADV) rescue therapy and the feasibility of lamivudine (LAM) discontinuation in LAM-resistant chronic hepatitis B (CH-B) patients who had attained a virological response (VR) with LAM + ADV combination therapy. **Methods:** The VR and virological breakthrough (VBT) were analyzed in 106 consecutively enrolled LAM-resistant CH-B patients who received ADV rescue therapy during a mean follow-up period of 55.2 months. Seventy-four patients achieved VR, and were divided into the LAM-discontinuation group (n = 39) and the LAM-continuation group (n = 35). The VR and VBT between the 2 groups were compared. **Results:** For all 106 LAM-resistant CH-B patients, the overall cumulative probabilities of VR at 1, 2, 3 and 5 years of ADV rescue therapy were 40.6, 55.7, 64.6 and 81.3%, respectively. The cumulative probabilities of VBT at 1, 2, 3 and 5 years were 0, 2.9, 8.8 and 13.9%, respectively. Whether they discontinued or continued LAM after

achieving VR on LAM + ADV therapy, VR and VBT were not significantly different during a mean follow-up period of 40.4 months. **Conclusions:** There was a good long-term VR with ADV rescue therapy for LAM-resistant CH-B patients. Moreover, discontinuing LAM was found to be feasible for patients who attained VR during ADV + LAM therapy.

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Introduction

A persistently high level of serum hepatitis B virus (HBV) DNA is associated with an increased risk of cirrhosis, hepatocellular carcinoma and liver-related mortality [1–4]. As a major therapeutic tool for chronic hepatitis B (CH-B), nucleos(t)ide analogs suppress HBV replication and lead to a virological response (VR), defined as an undetectable level of serum HBV DNA, which improves long-term prognosis [5–8]. However, nucleos(t)

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ide analogs do not eradicate HBV, and therefore long-term therapy is required, which can result in the emergence of drug resistance and high costs for drug administration [9].

Adefovir dipivoxil (ADV) is effective against both wild-type and lamivudine (LAM)-resistant HBV in compensated and decompensated patients [5, 6, 10–14]. For LAM-resistant patients, adding ADV on to previous LAM therapy (i.e. LAM + ADV combination therapy) showed significantly less ADV resistance than ADV single therapy (LAM to ADV switch therapy) [15–20]. However, it has not yet been studied if once a VR is attained with LAM + ADV combination therapy, administration of LAM should be combined indefinitely or could actually be discontinued [21–24]. Moreover, LAM and ADV are no longer first-line drugs for CH-B patients in many countries since the introduction of entecavir (ETV) and tenofovir (TDF), both of which show higher antiviral potency and a higher resistance barrier than LAM or ADV.

In South Korea, reimbursement of the cost of LAM for LAM-resistant patients on the combination therapy was not permitted by National Health Insurance until a few years ago. So, according to their economic conditions, these patients had only the option of self-paid LAM and insurance-covered ADV for the LAM + ADV combination therapy or a discontinuation of LAM with insurance-paid ADV monotherapy [23, 25]. Therefore, after achieving VR, many were willing to discontinue the self-paid LAM. Although the system of partial reimbursement was recently changed to include full coverage of the combination therapy, this previous restriction in health insurance presented a unique opportunity to compare the antiviral efficacy of a LAM-discontinuation group, i.e. patients on ADV single-maintenance therapy and a LAM-continuation group, i.e. patients on an indefinite combination of LAM + ADV after attaining VR.

The aims of this study were to clarify the long-term antiviral efficacy of ADV rescue therapy for LAM-resistant CH-B and to investigate the feasibility of discontinuing LAM after achieving VR in the LAM-resistant CH-B patients who were treated with the LAM + ADV combination therapy until a VR was achieved.

Materials and Methods

Patients

A total of 363 LAM-resistant CH-B patients were treated with ADV from June 2004 to December 2009 at the Seoul National University Bundang Hospital and then followed up until June 2013. After excluding patients with decompensated cirrhosis or hepato-

cellular carcinoma at the initiation of ADV therapy, patients whose therapy was of short duration (<12 months) and cases of poor compliance, 209 patients received ADV therapy for >12 months, with a compliance rate of >80% by the pill-count method which was checked at every visit to the outpatient clinic. Cases where there was poor compliance after 12 months of ADV therapy (n = 11), readministration of LAM after an interval from the initiation of ADV therapy (n = 16), incomplete baseline data due to ADV administration having been started in another hospital (n = 32) and therapy consisting of ADV single-therapy only (n = 44) were excluded at this point.

The final subjects of this study were therefore 106 patients who received ADV + LAM combination therapy after a resistance to LAM had emerged and the biochemical aggravation indicated by alanine aminotransferase (ALT) levels were >2 times the upper limit of normal. VR was achieved in 74 patients, who were divided into the LAM-discontinuation group (n = 39) and the LAM-continuation group (n = 35). The baseline characteristics, VR and virological breakthrough (VBT) of these 2 groups were compared. This study was approved by the institutional review board of this hospital, and informed consent was waived because of the retrospective analysis of medical records.

Methods

The clinical data were retrieved retrospectively from electronic medical records and entered into a computerized database. They included serum HBV DNA level, HBeAg status and biochemical liver function tests. Usual practice was for each patient to be followed up within 3 months of antiviral therapy and at intervals of 1–4 months thereafter. Serum HBV DNA level was quantified using signal amplification by the 7300 real-time PCR system (Applied Biosystems, Foster City, Calif., USA) and the detection limit was 60 IU/ml of serum in this hospital. Serum HBeAg and HBeAb were examined by ELISA (Abbott Laboratories, Chicago, Ill., USA).

Evaluation of Antiviral Response

VR after ADV therapy was defined as a serum HBV DNA reduction in the undetectable levels (<60 IU/ml). HBeAg loss and seroconversion (for HBeAg-positive patients) and biochemical response as serum ALT levels decreased to the normal range (up to 40 IU/l) at the end of follow-up were analyzed. VBT was defined as an increase in the level of HBV DNA of at least 1 log₁₀ IU/ml from the nadir, and was repeatedly examined at intervals of at least 1 month intervals during the ADV treatment. Virological relapse was defined as detection of HBV DNA after achieving VR, but <1 log₁₀ IU/mL [26]. All patients experiencing a confirmed VBT underwent viral resistance mutational analysis, which was performed by PCR and a direct sequencing method.

Statistical Analysis

Data were expressed as the mean with standard deviation (SD) for discrete variables and as counts and percentages for qualitative variables. Continuous variables were compared with the Student t test and categorical variables were assessed using the χ^2 test, the Fisher exact test or the Mann-Whitney U test. The cumulative probabilities of achieving VR and VBT were assessed using the Kaplan-Meier method and the log-rank test. A logistic regression model was used for univariate and multivariate analysis for searching independent predictors of VR or VBT. A p value <0.05 for

Table 1. Baseline characteristics of 106 patients with LAM-resistant CH-B treated with LAM + ADV combination therapy

Clinical characteristics	LAM + ADV
Age, years	48.5±10.1
Male	73 (68.9%)
Body mass index, kg/m ²	24.5±2.9
Compensated liver cirrhosis	32 (30.2%)
HBeAg positivity	79 (74.5%)
HBV DNA, log IU/ml	6.23±1.24
ALT, IU/l	259.6±393.5
Albumin, g/dl	4.2±0.4
Bilirubin, mg/dl	1.2±1.7
Platelet count, ×10 ³ /mm ³	164.1±59.8
Duration of prior LAM therapy, months	26.7±14.8
Duration of ADV therapy, months	55.2±16.8
VR at last follow-up	73 (68.8%)
VBT at last follow-up	8 (7.5%)
Virological relapse after VR	17 (21.5%)

Values are n (%) or mean ± SD.

2-sided tests was considered to be statistically significant. Data handling and analysis were performed by SPSS software for Windows, version 18 (SPSS Inc., Chicago, Ill., USA).

Results

The Overall Antiviral Efficacy of ADV Rescue Therapy for LAM-Resistant CH-B

The clinical features and antiviral efficacy of ADV rescue therapy for 106 patients are summarized in table 1. The overall cumulative probabilities of VR at 1, 2, 3 and 5 years of ADV treatment were 40.6, 55.7, 64.6 and 81.3%, respectively (fig. 1a), while the cumulative probabilities of VBT at 1, 2, 3 and 5 years were 0, 2.9, 8.8 and 13.9%, respectively (fig. 1b).

Clinical variables were analyzed to search for predictors of VR by means of a logistic regression model (table 2). Among the variables, baseline HBV-DNA levels [$<6 \log \text{ IU/ml}$; odds ratio (OR) 2.85, $p = 0.017$] and HBeAg positivity (OR 0.33, $p = 0.033$) were significantly associated with VR on the univariate analysis. The multivariate analysis using a step-wise logistic regression model showed that the baseline HBV-DNA level was an independent predictor for the VR of ADV therapy (OR 2.49, $p = 0.041$).

ADV treatment was well tolerated. The overall median serum creatinine level was $1.00 \pm 0.1 \text{ mg/dl}$ at the baseline, and $0.97 \pm 0.2 \text{ mg/dl}$ at the last follow-up. Only 1/106

Fig. 1. The overall antiviral efficacy of LAM + ADV combination therapy in 106 LAM-resistant CH-B patients. **a** Overall cumulative probability of the VR. **b** Overall cumulative probability of the VBT. VR was defined as an undetectable serum HBV DNA level $<60 \text{ IU/ml}$ and VBT as an increase in serum HBV DNA level of at least $1 \log_{10} \text{ IU/ml}$ from the nadir.

patients (0.9%) had an increase in serum creatinine level of $>0.5 \text{ mg/dl}$ during ADV therapy. An elevation in creatinine level from 1.1 to 2.2 mg/dl was observed in this patient after 37 months of ADV therapy; after dose reduction, their renal function improved.

Table 2. Univariate and multivariate analysis of predictors associated with the VR of ADV rescue therapy in 106 LAM-resistant CH-B patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (per year)	1.01 (0.98–1.05)	0.517		
Male gender	0.48 (0.21–1.10)	0.084		
Cirrhosis (yes vs. no)	1.26 (0.58–2.75)	0.560		
HBeAg positivity	0.33 (0.12–0.91)	0.033 ^a	0.39 (0.14–1.10)	0.075
HBV DNA (log IU/ml <6)	2.85 (1.21–6.72)	0.017 ^a	2.49 (1.04–5.98)	0.041 ^a
Albumin (per g/dl)	1.10 (0.45–2.74)	0.831		
Bilirubin (per mg/dl)	0.99 (0.82–1.18)	0.869		
Creatinine (per mg/dl)	0.34 (0.61–1.87)	0.215		
ALT				
<2 times UNL	1	0.840		
2–5 times UNL	1.04 (0.45–2.38)	0.923		
≥5 times UNL	1.29 (0.52–3.18)	0.581		
Prothrombin time (INR)	1.05 (0.82–1.33)	0.709		
Platelets (per 10 ³ /μl)	1.00 (0.99–1.01)	0.313		
ADV treatment				
Switch therapy	1			
Add-on therapy	2.03 (0.96–4.26)	0.063		

CI = Confidence interval. The VR was defined as undetectable serum levels of HBV DNA using a branched DNA assay (a low limit of quantification, <60 IU/ml).

^a $p < 0.05$.

Feasibility of Discontinuing LAM after VR during LAM + ADV Combination Therapy

Of the 74 patients who had achieved VR during LAM + ADV combination therapy, 39 discontinued LAM within 12 months of the VR (LAM-discontinuation group) and 35 continued LAM + ADV for >12 months after VR (LAM-continuation group). VR was confirmed by the negative HBV DNA levels on the repeated tests done at intervals of 1–4 months. Comparison of the baseline clinical characteristics and treatment outcomes between the 2 groups are summarized in table 3. There was no significant difference in the baseline characteristics and therapeutic outcomes, except in the duration of LAM treatment after VR. One patient from each group experienced VBT at the last follow-up, and maintenance of the VR until then was found in 35 patients (89.7%) in the LAM-discontinuation group and in 33 (94.3%) in the LAM-continuation group ($p = 0.677$). The cumulative probabilities of virological relapse in the LAM-discontinuation group were not statistically different from those in the LAM-continuation group (log-rank test, $p = 0.442$; fig. 2). Two patients displaying VBT received ETV rescue therapy, either as ETV

only or ETV + ADV combination therapy. Of 4 patients showing a virological relapse, 2 received TDF and the other 2 added LAM to ADV monotherapy.

Discussion

In this study, ADV rescue therapy for LAM-resistant CH-B ($n = 106$, mean therapy duration 55.2 months) resulted in a 5-year cumulative probability of VR and VBT of 81.3 and 13.9%, respectively. At the last follow-up, ALT normalization was found in 82.1% of the patients. After achieving VR during LAM + ADV combination therapy ($n = 74$), whether LAM was continued or not, the VR and VBT did not change; this suggests that LAM discontinuation is feasible in these patients.

The rescue options for LAM-resistant CH-B patients in Korea until 2012 were LAM + ADV combination, ‘LAM to ADV switch’ and ‘LAM to 1 mg of ETV switch’ therapy [18–20]. The option of LAM + ADV combination therapy was superior to the ‘LAM to ADV switch’ or ‘LAM to 1 mg of ETV switch’ therapy in previous reports [13–15, 17–19, 27]. However, since 2013, TDF has been

Table 3. Comparison of clinical characteristics and VR, VBT and virological relapse rates between the LAM-continuation group and the LAM-discontinuation group after achieving a VR on LAM + ADV combination therapy

Variables	LAM-discontinuation group ^a (n = 39)	LAM-continuation group ^b (n = 35)	p value
Age, years	51.0±9.0	46.7±10.5	0.063
Male/female	22/17	26/9	0.108
HBeAg positivity	24 (61.5)	26 (74.3)	0.242
Baseline HBV DNA, log IU/ml	5.91±1.29	6.13±1.30	0.471
ALT, IU/l	261.9±286.1	229.6±424.3	0.700
Creatinine, mg/dl	0.95±0.29	1.07±0.14	0.117
Duration of total ADV treatment, months	55.4±17.1	58.9±12.8	0.315
Duration of LAM treatment after VR, months	4.9±3.1	23.7±10.0	<0.001
HBeAg loss at last follow-up	14 (35.9)	14 (40.0)	0.716
HBeAb seroconversion at last follow-up	5 (12.8)	6 (17.1)	0.602
HBV DNA, log IU/ml at last follow-up	1.95±0.66	1.91±0.54	0.773
Creatinine level, mg/dl at last follow-up	0.95±0.24	0.98±0.18	0.573
VR at last follow-up	35 (89.7)	33 (94.3)	0.677
Biochemical response at last follow-up	35 (89.7)	28 (80.0)	0.239
VBT at last follow-up	1 (2.6)	1 (2.9)	0.939 ^d
Virological relapse ^c at last follow-up	3 (7.7)	1 (2.9)	0.362 ^d

Values denote n (%) or a mean ± SD.

^a LAM was discontinued according to the LAM overlap period of 12 months after achieving a VR.

^b LAM was continued according to the LAM overlap period of 12 months after achieving a VR.

^c Virological relapse: HBV DNA detectable after achieving a VR.

^d Analysis was performed by Mann-Whitney U test.

Fig. 2. The comparison of VR and virological relapse between the LAM-continuation group (n = 39) and the LAM-discontinuation group (n = 35) after achieving VR on LAM + ADV combination therapy. **a** Comparison of cumulative probabilities of VR showed no significant difference between the LAM-continuation group (solid line) and the LAM-discontinuation group (dotted line). p =

0.065, log-rank test. **b** Comparison of cumulative probabilities of virological relapse showed no significant difference between the LAM-continuation group (solid line) and the LAM-discontinuation group (dotted line) after achieving VR on LAM + ADV combination therapy. p = 0.442, log-rank test.

the best option for the rescue of LAM resistance, either as a TDF monotherapy or LAM + TDF in combination, with recent studies showing these to be comparable [28, 29].

Toyama et al. [30] reported that the overall VR at 4 years of ADV rescue therapy for LAM-resistant CH-B was 90.8%, and the rate of HBeAg loss at the end of follow-up was 34.0%. In this study, ADV rescue therapy for LAM-resistant CH-B showed cumulative probabilities of VR of 40.6, 55.7, 64.6 and 81.3% at 1, 2, 3 and 5 years, respectively, and of VBT of 0, 2.9, 8.8 and 13.9% at 1, 2, 3 and 5 years, respectively. In the HBeAg-positive patients (n = 79), the rate of HBeAg loss and of HBeAb seroconversion were 44.3 and 17.7%, respectively.

In previous studies, the predictors for VR to ADV therapy in nucleos(t)ide-naïve and LAM-resistant CH-B patients have been reported to be female gender, negative HBeAg, lower baseline HBV DNA, higher ALT level and genotype D (rather than A) [5, 11–15, 27, 31, 32]. Our results were partially in agreement, with the viral load before ADV therapy being independent predictors for the VR, whereas HBeAg positivity and ALT level were not significant predictors, probably because HBeAg positivity is strongly correlated with viral load. Therefore, ADV therapy should be initiated as soon as possible after confirmation of resistance to LAM during LAM therapy before elevation of HBV DNA levels occurs. Renal impairment during ADV therapy was observed in only 1 of all of the 106 patients (0.9%) in our study, suggesting that ADV rescue therapy has a good safety profile.

To find out the feasibility of discontinuing LAM in patients on LAM + ADV combination therapy once VR had been achieved, we compared the VR, VBT and virological relapse of the LAM-discontinuation group and the LAM-continuation group. The results showed no significant

between-group differences in the maintenance of these, so we concluded that LAM could be discontinued after VR was confirmed. This was in agreement with those of a recent study by Kim et al. [33], reporting a VR rate of 94.4% to have been sustained once LAM had been discontinued in CH-B patients with LAM + ADV combination therapy; however, the follow-up period of 2 years in their study was relatively short. The rationale for LAM discontinuation after VR was based on the supposition that ADV alone can control a very low titer of both LAM-resistant and wild-type HBV at the status of VR, and that the LAM discontinuation may reduce the LAM-resistant viral subpopulation, possibly further reducing the development of multidrug resistance. Moreover, medical costs and potential long-term adverse effects related to indefinite LAM combination therapy are reduced.

The limitations of our study were that it was retrospective and a single-center experience as well as the period of administration of the LAM combination therapy being so variable (a mean overlap period of 4.95 months) and the number of patients in the LAM-discontinuation group being small. Although the sample size of this study was small, enrollment of more patients was impossible because TDF became available in South Korea in January 2013. However, our subjects were a consecutively enrolled cohort without arbitrary selection, and most of the required data for this study were available in the medical records.

In conclusion, long-term ADV rescue therapy for LAM-resistant CH-B showed a good antiviral response, and the independent predictor for the VR was a lower HBV DNA titer at baseline. LAM could be discontinued for LAM resistant patients who achieved VR during LAM + ADV combination therapy. Long-term follow up study is warranted to confirm our results.

References

- 1 Fung SK, Wong F, Hussain M, Lok AS: Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. *J Viral Hepat* 2004; 11:432–438.
- 2 Lok AS, McMahon BJ: Chronic hepatitis B: Update of recommendations. *Hepatology* 2004;39:857–861.
- 3 Degertekin B, Lok AS: Update on viral hepatitis: 2008. *Curr Opin Gastroenterol* 2009;25: 180–185.
- 4 Lok AS, McMahon BJ: Chronic hepatitis B: update 2009. *Hepatology* 2009;50:661–662.
- 5 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Arterburn S, Xiong S, Currie G, Brosgart CL: Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673–2681.
- 6 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Brosgart CL, Borroto-Esoda K, Arterburn S, Chuck SL: Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743–1751.
- 7 Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, Gardner S, Gray DF, Schiff ER: Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–117.
- 8 Lee YS, Suh DJ, Lim YS, Jung SW, Kim KM, Lee HC, Chung YH, Lee YS, Yoo W, Kim SO: Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. *Hepatology* 2006;43:1385–1391.
- 9 Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, Lim SG, Wu PC, Dent JC, Edmundson S, Condreay LD, Chien RN: Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;33: 1527–1532.

- 10 Peters MG, Hann HW, Martin P, Heathcote EJ, Buggisch P, Rubin R, Bourliere M, Kowdley K, Trepo C, Gray DF, Sullivan M, Kleber K, Ebrahimi R, Xiong S, Brosgart CL: Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004;126:91–101.
- 11 Liu CJ, Kao JH, Chen PJ, Chen TC, Lin FY, Lai MY, Chen DS: Overlap lamivudine treatment in patients with chronic hepatitis B receiving adefovir for lamivudine-resistant viral mutants. *J Viral Hepat* 2006;13:387–395.
- 12 Buti M, Elefsiniotis I, Jardi R, Vargas V, Rodriguez-Frias F, Schapper M, Bonovas S, Esteban R: Viral genotype and baseline load predict the response to adefovir treatment in lamivudine-resistant chronic hepatitis B patients. *J Hepatol* 2007;47:366–372.
- 13 Inoue J, Ueno Y, Wakui Y, Niitsuma H, Fukushima K, Yamagiwa Y, Shiina M, Kondo Y, Kakazu E, Tamai K, Obara N, Iwasaki T, Shimosegawa T: Four-year study of lamivudine and adefovir combination therapy in lamivudine-resistant hepatitis B patients: influence of hepatitis B virus genotype and resistance mutation pattern. *J Viral Hepat* 2011;18:206–215.
- 14 Chen CH, Wang JH, Lu SN, Hu TH, Hung CH, Chang MH, Changchien CS, Lee CM: Characteristics of adefovir resistance in patients with or without lamivudine-resistant hepatitis B virus treated with adefovir: a 4-year experience. *Liver Int* 2011;31:206–214.
- 15 Chen EQ, Wang LC, Lei J, Xu L, Tang H: Meta-analysis: adefovir dipivoxil in combination with lamivudine in patients with lamivudine-resistant hepatitis B virus. *Virol J* 2009;6:163.
- 16 Liaw YF, Lee CM, Chien RN, Yeh CT: Switching to adefovir monotherapy after emergence of lamivudine-resistant mutations in patients with liver cirrhosis. *J Viral Hepat* 2006;13:250–255.
- 17 Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ: Adding-on versus switching to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology* 2007;45:307–313.
- 18 Cho SW, Cho YJ, Cheong JY, Lee MH, Jeon SJ, Lee YC, Lim SG, Kang CJ: Add on lamivudine to adefovir monotherapy for the treatment of lamivudine-resistant chronic hepatitis B patients. *Korean J Gastroenterol* 2010;56:83–89.
- 19 Aizawa M, Tsubota A, Fujise K, Sato K, Baba M, Takamatsu M, Namiki Y, Ohkusa T, Tajiri H: Overlap/switch to adefovir monotherapy for lamivudine-resistant patients who responded to combination therapy: a pilot controlled study. *Intern Med* 2010;49:1067–1072.
- 20 Lee HC: Lamivudine and adefovir combination therapy in lamivudine-resistant HBeAg-positive chronic hepatitis B patients. *Korean J Med* 2009;77:713–715.
- 21 Fung SK, Chae HB, Fontana RJ, Conjeevaram H, Marrero J, Oberhelman K, Hussain M, Lok AS: Virologic response and resistance to adefovir in patients with chronic hepatitis B. *J Hepatol* 2006;44:283–290.
- 22 Marcellin P, Chang TT, Lim SG, Sievert W, Tong M, Arterburn S, Borroto-Esoda K, Frederick D, Rousseau F: Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2008;48:750–758.
- 23 Shin SR, Koh KC, Gwak GY, Choi MS, Lee JH, Paik SW, Yoo BC: A low viral load predicts a higher initial virologic response to adefovir in patients with lamivudine-resistant chronic hepatitis B. *Gut Liver* 2010;4:530–536.
- 24 Aizawa M, Tsubota A, Fujise K, Tatsuzawa K, Kono M, Hoshina S, Tajiri H: Clinical course and predictive factors of virological response in long-term lamivudine plus adefovir dipivoxil combination therapy for lamivudine-resistant chronic hepatitis B patients. *J Med Virol* 2011;83:953–961.
- 25 Jung YK, Yeon JE, Han WS, Kim JH, Kim JH, Park JJ, Kim JS, Bak YT, Yoo W, Hong SP, Kim SO, Kwon SY, Byun KS, Lee CH: Virologic response at 12 months of treatment predicts sustained antiviral efficacy in patients with adefovir-treated lamivudine-resistant chronic hepatitis B. *Gut Liver* 2010;4:212–218.
- 26 Liang Y, Jiang J, Su M, Liu Z, Guo W, Huang X, Xie R, Ge S, Hu J, Jiang Z, Zhu M, Wong VW, Chan HL: Predictors of relapse in chronic hepatitis B after discontinuation of anti-viral therapy. *Aliment Pharmacol Ther* 2011;34:344–352.
- 27 Chung GE, Kim W, Lee KL, Hwang SY, Lee JH, Kim HY, Jung YJ, Kim D, Jeong JB, Kim BG, Kim YJ, Yoon JH, Lee HS: Add-on adefovir is superior to a switch to entecavir as rescue therapy for lamivudine-resistant chronic hepatitis B. *Dig Dis Sci* 2011;56:2130–2136.
- 28 van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, Erhardt A, Huppe D, Stein K, Trojan J, Sarrazin C, Bocher WO, Spengler U, Wasmuth HE, Reinders JG, Moller B, Rhode P, Feucht HH, Wiedenmann B, Berg T: Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology* 2010;51:73–80.
- 29 Glyn F, Gill US, Alazawi W, Ross V, Kooner P, Marley R, Foster GR, Kennedy PTF: Efficacy of combination tenofovir plus lamivudine versus tenofovir monotherapy in patients with chronic hepatitis B virus (abstract). *Gut* 2011;60:A231.
- 30 Toyama T, Ishida H, Ishibashi H, Yatsushashi H, Nakamura M, Shimada M, Ohta H, Satoh T, Kato M, Hijioka T, Takano H, Komeda T, Yagura M, Mano H, Watanabe Y, Kobayashi M, Mita E: Long-term outcomes of add-on adefovir dipivoxil therapy to ongoing lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Hepatol Res* 2012;42:1168–1174.
- 31 Mitsui F, Tsuge M, Kimura T, Kitamura S, Abe H, Saneto H, Kawaoka T, Miki D, Hatakeyama T, Hiraga N, Imamura M, Kawakami Y, Aikata H, Takahashi S, Hayes CN, Igarashi H, Morimoto K, Shimizu M, Chayama K: Importance of serum concentration of adefovir for lamivudine-adeфовir combination therapy in patients with lamivudine-resistant chronic hepatitis B. *Antimicrob Agents Chemother* 2010;54:3205–3211.
- 32 Shakado S, Watanabe H, Tanaka T, Morihara D, Nishizawa S, Inomata S, Ueda S, Matsumoto T, Anan A, Takeyama Y, Irie M, Iwata K, Sohma T, Sakisaka S: Combination therapy of lamivudine and adefovir in Japanese patients with chronic hepatitis B. *Hepatol Int* 2008;2:361–369.
- 33 Kim MN, Lee CK, Ahn SH, Lee S, Kim SU, Kim DY, Kim HS, Han KH, Chon CY, Park JY: Maintaining remission in lamivudine-resistant patients with a virological response to adefovir add-on lamivudine after stopping lamivudine therapy. *Liver Int* 2013. DOI: 10.1111/liv.12437.