Original article

Long-term adefovir dipivoxil monotherapy for up to 5 years in lamivudine-resistant chronic hepatitis B

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Background: Large clinical studies assessing long-term adefovir dipivoxil salvage monotherapy in patients with lamivudine-resistant chronic hepatitis B (CHB) are lacking, particularly in patients positive for hepatitis B e antigen (HBeAg). We assessed the efficacy and resistance profile of adefovir dipivoxil monotherapy for up to 5 years in a large cohort of Korean patients with lamivudine-resistant CHB.

Methods: A total of 320 patients (81.3% HBeAg-positive; 100% genotype C) with confirmed genotypic lamivudine-resistant CHB were switched to adefovir dipivoxil 10 mg once daily. Liver function tests and HBV DNA were monitored every 3 months. Genotypic resistance to adefovir dipivoxil was performed in patients with detectable HBV DNA.

Results: The overall cumulative virological response rate at 5 years of adefovir dipivoxil therapy was 48.8%. The virological response rate was significantly higher in HBeAg-negative patients (62.0% versus 45.9%; *P*=0.010). Most cases of virological response (131/134, 97.8%) occurred within the first 36 months of therapy. The 5-year cumulative probability of genotypic resistance and virological breakthrough was 65.6% and 61.8%, respectively. Predictive factors for a virological response included baseline HBeAg seronegativity, HBV DNA≤8 $\log_{10}$ copies/ml and achievement of an on-treatment initial virological response.

Conclusions: Adefovir dipivoxil salvage monotherapy for lamivudine-resistant CHB resulted in a modest cumulative virological response rate at 5 years, which was associated with progressive antiviral resistance. Consequently, adefovir monotherapy is not preferable as a first-line strategy for lamivudine resistance where combination lamivudine plus adefovir dipivoxil therapy is available.

Introduction

Chronic HBV infection is an important public health problem that affects approximately 400 million people worldwide; it is a well-known risk factor for cirrhosis and hepatocellular carcinoma (HCC) [1]. Ongoing HBV replication with chronic inflammation is strongly associated with disease progression towards cirrhosis or HCC. Consequently, a primary goal of antiviral therapy is to potently and durably suppress serum HBV DNA levels [2,3].

Lamivudine (3TC) was one of the first nucleoside/nucleotide analogues used to treat chronic hepatitis B (CHB). Treatment with 3TC has been clearly shown to significantly reduce the incidence of hepatic decompensation and risk of HCC [4]. However, 3TC is associated with the progressive development of genotypic resistance (up to 70% after 5 years) at the YMDD motif [5]; thus, 3TC is no longer a preferred first-line antiviral agent.

Adefovir dipivoxil (ADV) was the second drug approved for treating CHB and has antiviral activity against both wild-type and 3TC-resistant HBV [6,7]. Although switching to ADV monotherapy might be an effective salvage option for treating 3TC resistance [8–10], subsequent studies have suggested that this strategy is associated with a suboptimal clinical course and increased risk of ADV resistance compared with combination ADV plus 3TC therapy [11–14]. The ADV mutations at rtA181V/T and rtN236T appeared to emerge earlier and more frequently with ADV

monotherapy, whereas combination ADV plus 3TC was unlikely to result in genotypic resistance to ADV [11–14]. On the basis of these results, the combination of ADV and 3TC has gained more support in managing 3TC-resistant CHB. However, most studies with combination therapy in this clinical setting have examined Caucasian patients with predominantly hepatitis B virus e antigen (HBeAg)-negative infection. Furthermore, the maximum reported follow-up duration of salvage ADV monotherapy was only 3 years. Thus, further evaluation of ADV monotherapy in 3TC-resistant patients in different clinical cohorts and with a longer duration of follow-up would be of value.

Combination therapy in the setting of previous 3TC resistance is currently not applied universally, owing to higher costs. In Korea, where CHB is endemic, ADV monotherapy is a common salvage regimen as the result of a limited national insurance reimbursement scheme. The aim of this study was to assess the antiviral efficacy and resistance profile of long-term salvage ADV monotherapy in a large cohort of Korean patients with 3TC-resistant CHB, the majority of whom were HBeAg-positive.

Methods

Patients

Data were analysed for all patients who were switched to ADV because of 3TC resistance since October 2003. The inclusion criteria for this study were age >16 years, serum hepatitis B virus surface antigen present ≥6 months, serum HBV DNA≥10^5 copies/ml, therapy with 3TC for at least 6 months, HBV genotype C, confirmed mutation at the YMDD motif and follow-up for at least 1 year on ADV therapy. Exclusion criteria were decompensated liver cirrhosis (history of ascites, encephalopathy, varices, serum total bilirubin level >2.5 mg/dl, serum albumin <3 mg/dl or prothrombin time >3 s longer than normal), serum creatinine level >1.5 mg/dl, previous oral antiviral treatment other than 3TC, treatment with immunomodulatory drugs, current corticosteroid usage, coinfection with HCV and HDV or HIV, serious concurrent medical illness, evidence of HCC or prior organ transplantation.

Study design

Patients received oral ADV (10 mg once daily) after switching from 3TC with an overlap period of <2 months. Patients were monitored with laboratory assays at baseline and every 3 months. From July 2006, all patients commencing salvage ADV monotherapy had yearly prospective genotypic resistance testing. In addition, the stored samples that had been collected before July 2006 were tested for ADV-resistant mutations. The follow-up period was defined as the interval up to the last clinical visit or when virological breakthrough to ADV monotherapy was detected, whichever occurred first. This study was approved by the local institutional review board and conducted in accordance with the principles set forth in the Declaration of Helsinki.

Laboratory assays

Routine biochemical tests, including measurements of alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, albumin, creatinine and prothrombin time were performed using a sequential multiple auto-analyser. HBeAg and antibodies against HBeAg were tested with enzyme-linked immunoassays (Dade Behring, Marburg, Germany). HBV DNA levels were quantified using a PCR assay on a COBAS TaqMan 48 analyser (Roche Molecular Systems, Branchburg, NJ, USA; lower detection limit 300 copies/ml). Genotypic resistance to 3TC or ADV was analysed using restriction fragment mass polymorphism (RFMP), as previously described [11,12,15–17]. Analytical sensitivities in detecting 3TC or ADV-resistant strains were estimated to be 300 copies/ml. The results of the RFMP assay were validated by 100% concordance with those obtained by repetitive direct sequencing.

End points and definitions

The primary end points of the study were the development of a virological response, virological breakthrough and genotypic resistance. A virological response was defined as an undetectable HBV DNA by PCR assay (<300 copies/ml) at any stage of therapy. Virological breakthrough was defined as an increase in HBV DNA≥1 $\log_{10}$ copies/ml from the treatment nadir after an initial decrease of ≥2 $\log_{10}$ copies/ml. Primary nonresponse was defined as a decrease in HBV DNA<2 $\log_{10}$ copies/ml after 6 months of therapy [18].

Secondary end points included biochemical response, initial virological response (IVR) and HBeAg seroconversion in HBeAg-positive patients. A biochemical response was defined as normalization of serum ALT; a biochemical breakthrough was defined as an increase of ALT≥ upper limit of normal (ULN; 49 IU/l) in conjunction with virological breakthrough after initial normalization [19]. An IVR was defined as HBV DNA<4 $\log_{10}$ copies/ml after 6 months of treatment [20,21]. Cirrhosis was defined based on ultrasonographic findings of a blunted, nodular liver edge accompanied by splenomegaly (>10 cm) with a low platelet count (<100 000/mm^3) [22,23].

Statistical analyses

Continuous variables were summarized as the median (range) or mean ±SD. Cumulative probabilities were estimated using Kaplan–Meier analysis; differences were tested using the log-rank test and multivariate analysis

was performed using stepwise Cox regression analysis. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The study included 320 patients with CHB who were switched to ADV monotherapy because of 3TC resistance (Table 1). The median age was 45 years (range 19–76). A total of 260 (81.3%) patients were HBeAg-positive. Cirrhosis was present in 93 (29.1%) patients. The median ADV treatment duration was 30 months (range 12–60): 320, 279, 164, 66 and 25 patients were treated with ADV for 12, 24, 36, 48 and 60 months, respectively. The mean ±SD baseline ALT was 209 ±231 IU/l and HBV DNA was 7.47 ±0.93 $\log_{10}$ copies/ml.

Virological response

Following 1 year of therapy, 73 (22.8%) patients had achieved undetectable HBV DNA. The annual additional occurrence of patients with undetectable HBV DNA at 2–5 years (months 24, 36, 48 and 60) was 45, 13, 3 and 0, respectively (Table 2). The cumulative probability of achieving an undetectable HBV DNA estimated from the Kaplan–Meier curve at 1–5 years was 16.9%, 34.8%, 44.0%, 48.8% and 48.8%, respectively. Interestingly, the ratio of patients who had a virological response through month 36 to those with a response through 60 months was 131/134 (97.8%). When comparing undetectable HBV DNA according to the HBeAg status, a significant difference was observed with a 62.0% cumulative probability in HBeAg-negative patients, compared with 45.9% in HBeAg-positive patients at month 60 (*P*=0.010; Figure 1). By contrast, there were 56 (17.5%) patients with primary non-response assessed at 6 months of therapy.

Biochemical response

ALT levels normalized in approximately 80% of patients at month 12. The annual additional occurrence of ALT normalization was 257, 8, 5, 1 and 0 with a cumulative probability of 80.3%, 83.0%, 87.3%, 89.5% and 89.5%, respectively (Table 2).

Serological response

The serological response was analysed among the 260 patients who were HBeAg-positive. Notably, HBeAg seroclearance and seroconversion were achieved mainly

Table 1. Baseline characteristics of patients

Characteristic	Value
Total patients, *n*	320
Median age, years (range)	45 (19–76)
Male sex, *n* (%)	246 (76.9)
Median prior 3TC duration, months (range)	23 (8–82)
HBeAg-positive, *n* (%)	260 (81.3)
Cirrhosis, *n* (%)	93 (29.1)
Median ADV treatment duration, months (range)	30 (12–60)
ADV treatment duration 12 months, *n*	320
ADV treatment duration 24 months, *n*	279
ADV treatment duration 36 months, *n*	164
ADV treatment duration 48 months, *n*	66
ADV treatment duration 60 months, *n*	25
YMDD mutation, *n* (%)	320 (100)
rtM204I alone, *n* (%)	81 (25.3)
rtM204I+rtM204V, *n* (%)	3 (0.9)
rtM204I+rtL180M, *n* (%)	95 (29.7)
rtM204V+rtL180M, *n* (%)	73 (22.8)
rtM204I+rtM204V+rtL180M, *n* (%)	68 (21.3)
Mean ALT, IU/l (±SD)[a]	209 (231)
Mean HBV DNA, $\log_{10}$ copies/ml (±SD)	7.47 (0.93)

[a]Alanine aminotransferase (ALT) reference range ≤40 IU/l. ADV, adefovir dipivoxil; HBeAg, hepatitis B e antigen; 3TC, lamivudine.

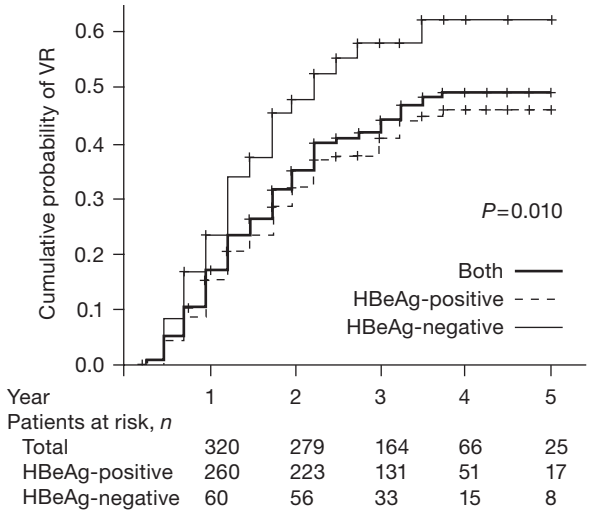
Table 2. Annual additional occurrence of virological, biochemical and serological response[a]

Patient response	ADV treatment duration				
	12 months	24 months	36 months	48 months	60 months
Undetectable HBV DNA					
Total, *n/N* (%)	73/320 (22.8)	45/279 (26.1)	13/164 (7.9)	3/66 (4.5)	0/25 (0.0)
HBeAg-positive, *n/N* (%)	53/260 (20.4)	36/223 (16.1)	11/131 (8.4)	2/51 (3.9)	0/17 (0.0)
HBeAg-negative, *n/N* (%)	20/60 (33.3)	9/56 (16.1)	2/33 (6.1)	1/15 (6.7)	0/8 (0.0)
Normalization of ALT					
Total, *n/N* (%)	257/320 (80.3)	8/279 (2.9)	5/164 (3.5)	1/66 (1.5)	0/25 (0.0)
HBeAg-positive, *n/N* (%)	212/260 (81.5)	5/223 (2.2)	3/131 (2.3)	0/51 (0.0)	0/17 (0.0)
HBeAg-negative, *n/N* (%)	45/60 (75.0)	3/56 (5.4)	2/33 (6.1)	1/15 (6.7)	0/8 (0.0)
HBeAg seroconversion, *n/N* (%)	19/260 (7.3)	12/223 (5.4)	3/131 (2.3)	1/51 (2.0)	0/17 (0.0)
HBeAg seroclearance, *n/N* (%)	33/260 (12.7)	19/223 (8.5)	10/131 (7.6)	1/51 (2.0)	0/17 (0.0)

[a]Values are given as the number of patients (*n*)/total number (*N*) together with the percentage. ADV, adefovir dipivoxil; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

within the first 36 months. Through 1–5 years, 33, 19, 10, 1 and 0 patients achieved seroclearance with a cumulative probability of 12.7%, 22.9%, 34.9%, 37.3% and 37.3%, respectively. Likewise, 19, 12, 3, 1 and 0 additional patients seroconverted after 1–5 years, which corresponded to 7.3%, 14.3%, 18.3%, 21.0% and 21.0% of the cumulative probability (Table 2). None of the patients in this study cleared hepatitis B surface antigen.

Figure 1. Cumulative probability of virological response according to HBeAg status



HBeAg, hepatitis B e antigen; VR, virological response.

Genotypic resistance

The number of patients who had detectable HBV DNA at 1–5 years was 247, 234, 151, 63 and 25, respectively, and prospective yearly assessment of genotypic resistance was commenced in July 2006 among patients who had detectable HBV DNA. The cumulative probability of genotypic resistance to ADV was calculated to be 4.4%, 18.4%, 34.3%, 52.3% and 65.6% at 1–5 years, respectively. Higher rates of genotypic resistance were noted in HBeAg-positive patients than in HBeAg-negative patients through 5 years (71.4% versus 45.6%, P=0.028; Table 3). There was no difference in cumulative probability of genotypic resistance according to the types of YMDD motif mutation at baseline (P=0.339). Among 112 patients who had genotypic resistance to ADV, substitution at rtA181V was only detected in 50 (44.6%) patients, at rtA181T only in 29 (25.9%) patients, at rtA181V+T in 3 (2.7%), at rtN236T only in 8 (7.1%) and at both rtA181V/T and rtN236T in 22 (19.7%) patients.

Virological breakthrough

The cumulative probability of developing virological breakthrough at 1–5 years was 1.6%, 20.7%, 39.5%,

Table 3. Additional occurrence and cumulative probability of virological breakthrough, genotypic resistance and combined virological breakthrough with genotypic resistance

Patient response	ADV treatment duration				
	12 months	24 months	36 months	48 months	60 months
Patients at risk, *n*	320	279	164	66	25
GR					
Additional occurrence (total=112)	14	41	32	18	7
Cumulative probability					
Total, %	4.4	18.4	34.3	52.3	65.6
HBeAg-positive, %	5.4	21.1	35.5	55.8	71.4
HBeAg-negative, %	0.0	8.9	28.2	37.8	45.6
VB					
Additional occurrence (total=116)	5	52	39	16	4
Cumulative probability					
Total, %	1.6	20.7	39.5	51.6	61.8
HBeAg-positive, %	1.9	21.7	41.5	53.9	66.7
HBeAg-negative, %	0.0	16.9	31.4	42.4	42.4
VB and GR					
Additional occurrence (total=85)	3	33	32	15	2
Cumulative probability					
Total, %	0.9	13.5	30.4	43.5	47.4
HBeAg-positive, %	1.2	13.5	38.5	45.0	50.4
HBeAg-negative, %	0.0	13.6	26.1	37.9	37.9

ADV, adefovir dipivoxil; GR, genotypic resistance; HBeAg, hepatitis B e antigen; VB, virological breakthrough.

51.6% and 61.8%, respectively (Table 3). There was no significant difference in virological breakthrough according to HBeAg status (P=0.122). However, over 5 years there was a tendency towards progressive virological breakthrough in HBeAg-positive patients; there was a cumulative probability of 1.9%, 21.7%, 41.5%, 53.9% and 66.7% compared with 0.0%, 16.9%, 31.4%, 42.4% and 42.4% in HBeAg-negative patients, respectively.

Genotypic resistance was analysed in all 116 patients who developed virological breakthrough. The cumulative probability of combined genotypic resistance and viorolgical breakthrough reached 47.4% through year 5. Among these 116 patients, 3TC was added in 71 (61.2%) patients, whereas ADV was switched to entecavir 1.0 mg monotherapy in 45 (38.8%) patients.

Durability

ADV was stopped and durability could be evaluated in 13 patients: 8 were HBeAg-positive and 5 HBeAg-negative. These patients had received ADV therapy for over 1 year after either HBeAg seroconversion and/or undetectable HBV DNA. Six HBeAg-positive patients (75%) and one HBeAg-negative patient (20%) maintained sustained virological response over a 1 year period; however, the remaining patients demonstrated a virological rebound of >4 $\log_{10}$ copies/ml within a 6 month period.

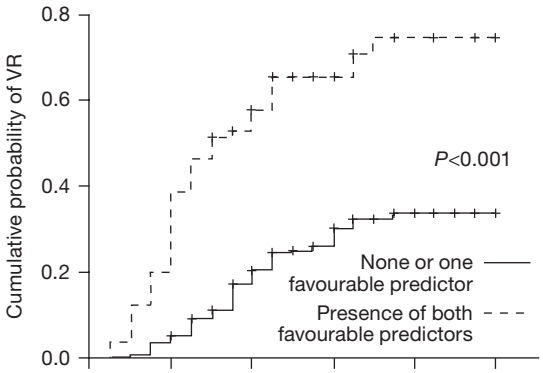
Prediction of virological response

Baseline HBeAg seronegativity (P=0.013), HBV DNA≤8 $\log_{10}$ copies/ml (P=0.031) and on-treatment IVR (144/320 [45.0%]; P<0.001) were significant predictors of a virological response on univariate analysis. On multivariate analysis with baseline factors, HBeAg seronegativity remained significant (P=0.028), with a trend observed with HBV DNA≤8 $\log_{10}$ (P=0.084). In HBeAg-positive patients, a significant difference in virological response was noted in patients with two favourable predictors (baseline HBV DNA≤8 $\log_{10}$ copies/ml and achievement of IVR; 80/260 [30.8%]) versus those with either or none (180/260 [69.2%] P<0.001; Figure 2). The cumulative probability of a virological response in patients with both predictors was 38.7%, 57.6%, 65.4%, 74.4% and 74.4% at 1–5 years, respectively. Similarly, HBeAg-negative patients with both predictors had a significantly higher virological response (P=0.036), with a cumulative probability of 74.9% at month 60.

Prediction of virological breakthrough

Baseline predictors of virological breakthrough on both univariate and multivariate analysis included HBV DNA>8 $\log_{10}$ copies/ml (P=0.014) and ALT level <2 ULN (P<0.001), which presumably resulted from the lack of immune response. HBeAg-positive patients with both baseline predictors had a significantly higher risk of virological breakthrough, with a cumulative probability of 2.8%, 26.3%, 50.7%, 62.6% and 73.5% in comparison to 0.0%, 17.2%, 17.2%, 29.7% and 41.4% in patients with either or none (P=0.001) at 1–5 years, respectively. A similar tendency was seen in HBeAg-negative patients showing virological breakthrough in 62.0% with both predictors versus 20.8% with either or none through month 60 (P=0.045).

Figure 2. Comparison of the virological response in HBeAg-positive patients according to the presence of both favourable predictors and the absence of either



Year	1	2	3	4	5
Patients at risk, *n*					
Total	260	177	99	38	11
Both favourable predictors	80	48	15	4	1
None or one favourable predictor	180	129	84	34	10

Favourable predictors of virological response (VR) in patients positive for hepatitis B e antigen (HBeAg) are initial HBV DNA≤8 $\log_{10}$ copies/ml and achievement of an initial VR.

Safety and clinical events

The majority of patients tolerated the drug well. The ADV dose was reduced to 10 mg on alternate days in 7 (2.2%) patients, because the serum creatinine increased to >0.5 mg/dl from baseline. In these patients, the serum creatinine level did not increase further after dose adjustment. No other significant adverse effects related to ADV were observed.

During ADV monotherapy, decompensated liver cirrhosis with ascites developed in 2 (1.0%) patients who had preserved liver function initially. Both patients were HBeAg-positive with continuous detectable HBV DNA despite ADV salvage monotherapy. In addition, 8 (2.5%) patients developed HCC; of these, 7 (87.5%) had cirrhosis and 5 (62.5%) had undetectable HBV DNA at the time of diagnosis of HCC.

Discussion

This is the first study in a large cohort of Asian patients with 3TC-resistant CHB to assess the long-term efficacy of ADV switch monotherapy. All patients were Korean and had HBV genotype C infection. The overall cumulative virological response rate at month 60 was 48.8%. The long-term virological response rate was significantly higher in HBeAg-negative patients (62.0% versus 45.9%; P=0.010), which is consistent with previous integrated studies [14,20,24–27]. Nevertheless, these results are inferior to previous studies with ADV plus 3TC combination therapy, which reported an undetectable HBV DNA in 82–100% of patients [14,24,27].

ADV monotherapy was associated with a high and progressive risk of both virological breakthrough and genotypic resistance in this study, reaching up to 61.8% and 65.6% at year 5, respectively. This study is the first to provide 5-year genotypic resistance rates in which the data through year 2 are in accordance with previous studies reporting approximately 20% genotypic resistance [11,12,20,28,29]. Such high rates of resistance are discouraging compared with studies of ADV plus 3TC combination therapy in HBeAg-negative patients, where genotypic resistance is <4% at year 4 [14,24,26]. Although no conclusive long-term results of resistance profiles with ADV plus 3TC combination therapy have been reported in HBeAg-positive patients with 3TC-resistance, the rates of resistance in our study are also higher than those reported in studies evaluating salvage entecavir monotherapy, which reported a rate of 51% at year 5 [30,31]. The higher rates of resistance with ADV might be attributable to its relatively lower degree of HBV DNA reduction [32].

The predictors of achieving a virological response were evaluated in this study. In addition to HBeAg status, two additional factors were found to be significant: initial HBV DNA≤8 $\log_{10}$ copies/ml and achievement of an IVR. When HBeAg-negative patients had both predictive factors, the virological response increased to 74.9% at month 60. Similarly, in HBeAg-positive patients, the virological response rate at month 60 in patients with both factors and with either or none was 74.4% versus 33.8%, respectively (P<0.001). Notably, long-term, large-scale data on ADV plus 3TC combination therapy in HBeAg-positive patients are scarce, except for a recent study by Yatsuji *et al.* [27] that reported a virological response of 68% through month 24 and 78% through month 36. Hence, ADV plus 3TC combination therapy also appears superior to ADV monotherapy in HBeAg-positive CHB. Consequently, salvage ADV monotherapy for 3TC resistance should not be considered a first-line therapy and, if necessary, should ideally be limited only to patients with favourable predictive factors in areas where medical resources are limited.

Interestingly, a virological response was achieved in most cases within the first 36 months of therapy, after which a plateau was observed. As described previously, of the 134 patients who achieved a virological response, 131 (97.8%) patients reached this through month 36. This suggests that little antiviral effect should be expected after 36 months. Similarly, few HBeAg-positive patients developed HBeAg seroconversion after month 36. By contrast, virological breakthrough increased linearly over time.

Limitations of this study were its mainly retrospective design and the fact that evaluation for genotypic resistance was only regularly performed after July 2006. A significant number of patients was excluded from analysis because of progressive virological breakthrough, resulting in a median follow-up duration of only 30 months and the relatively small number of patients over 4 years. The higher rate of genotypic resistance might be associated with the ultrasensitive RFMP method for detecting ADV-resistant mutations. The other potential limitation was that there was no ADV plus 3TC combination arm for direct comparison.

In summary, this study provides the first extensive, long-term, large-scale ADV monotherapy data in 3TC-resistant patients, especially in patients with HBeAg-positive CHB. The antiviral efficacy of ADV monotherapy was limited and expected mainly within the first 36 months. Predictive factors for antiviral efficacy included baseline HBeAg serostatus, HBV DNA≤8 $\log_{10}$ copies/ml and achievement of an on-treatment IVR. The overall rates of virological breakthrough and genotypic resistance with ADV monotherapy were inferior to those obtained for the ADV plus 3TC combination reported in other studies. Therefore, ADV monotherapy should not be used as a first-line rescue therapy unless medical resources and cost are a major factor. Further investigation of response rates, resistance profiles and cost-effectiveness of ADV salvage monotherapy versus combination therapy is warranted in 3TC-resistant patients, particularly in those who are HBeAg-positive. These regimens should include newer and more potent drugs.

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Disclosure statement

The authors declare no competing interests.

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