# Comparison of the 48-week efficacy of Lamivudine plus Adefovir or Entecavir monotherapy in patients with HBeAg negative hepatitis following Lamivudine treatment failure

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**Abstract**

***Aims* : To compare the efficacy of treatment with lamivudine (LAM) plus adefovir (ADV) or entecavir (ETV) monotherapy in LAM treatment failure patients with HBeAg negative chronic hepatitis B (CHB) patients during 48 weeks of therapy.**

***Patients and Methods* : Thirty patients with HBeAg negative CHB were enrolled in the study. The serum levels of HBV DNA, HBsAg/HBsAb, and ALT were assessed by enzyme-linked immunosorbent assay at 0, 12, 24, 36, and 48 weeks.**

***Results* : The rate of undetectable HBV DNA in the LAM+ADV group was 100%, which was higher than the ETV group at 48 weeks (73.33%, $\chi^2 = 4.615$, P = 0.032). Multivariate analysis using the Cox proportional hazards model showed that therapy with LAM+ADV or baseline levels of HBV DNA <$10^7$ copies/ml were independent predictive factors for undetectable HBV DNA rates in all patients (RR: 2.488, P = 0.042; RR: 0.201, P = 0.035).**

***Conclusions* : During the 48 weeks of treatment in patients with HBeAg negative CHB, LAM plus ADV suppressed HBV replication more effectively than ETV monotherapy. In addition, no virologic breakthrough was detected in the LAM add-on ADV group. Additionally, therapy with LAM+ADV or baseline levels of HBV DNA < $10^7$copies/ml were independent predictive factors for undetectable HBV DNA rates in patients.** (Acta gastroenterol. belg., **2019**, 82, **31-34**).

**Key words :** Adefovir, Entecavir, HBeAg negative hepatitis

## Introduction

It is well known that HBV replication plays an important role in HBV-related diseases, such as hepatitis, cirrhosis, and hepatocelluar carcinoma. Anti-viral treatment can reduce HBV-related morbidity or mortality. Currently established effective antiviral drugs approved for the treatment of HBV infection in China include recombinant interferons, such as interferon-α and its pegylated formulation, and the nucleos(t)ide analogues (NAs) lamivudine (LAM), adefovir (ADV), telbivudine (LDT), entecavir (ETV), and tenofovir (TDF) (1). Pegylated-interferon is an immune-modulatory agent that works mainly by enhancing the innate immune response. Pegylated-interferon treatment has a finite duration without induction of drug resistance, but only a limited number of patients achieve a sustained virologic response to therapy (2). Alternatively, the NAs work mainly by inhibiting HBV DNA polymerase activity and can achieve higher rates of viral replication suppression but require a long-term process with a potential risk of drug resistance.

LAM, first approved in 1998, has been in application for more than ten years. Research reports suggested that LAM has high potency in delaying disease progression when used in the treatment of chronic hepatitis B (CHB) patients. However, in CHB patients that underwent LAM treatment, the resistance rates at one, two, three, four, and five years were 14.7% (4.8%-23.5%), 37.8% (14.3%-65.9%), 49.8% (30.2%-70.5%), 62.0% (52.0%-67.0%), and 70.8%, respectively. In addition, the resistance rates were observed to rise with extended LAM treatment (3). Therefore, in patients with LAM-resistance, it is advisable to promptly add or change to other NAs to inhibit HBV replication.

Adding ADV or switching to other oral antiviral drugs with high genetic barriers to HBV can effectively inhibit HBV replication. Many studies have shown that LAM plus ADV can effectively rescue LAM-resistant CHB patients and obtain low viral breakthrough. ETV is a recommended first-line therapy for CHB in the current guidelines because of its high potency in viral suppression and higher barrier against resistance. It was demonstrated that ETV can provide high efficiency and rapid viral suppression for CHB patients when administered in a 240-week course (4).

At present, data on patients with HBeAg-negative CHB following LAM-treatment failure are limited. The aim of this study was to investigate the efficacy of LAM plus ADV or switching to ETV monotherapy in LAM treatment-failure patients with HBeAg-negative CHB and high viral levels of HBV DNA.

## Materials and methods

### *Patients and treatment strategy*

Between September 2010 and January 2016, 30 HBeAg-negative hepatitis patients with LAM treatment failure were enrolled in this study. Inclusion criteria were: 1) diagnosis met the "guide to prevention and

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treatment of chronic hepatitis of China in 2015" (5) ; 2) a history of LAM treatment failure ; 3) at least 18 years old ; 4) HBV DNA baseline levels >10 (6) copies/ml ; 5) ALT levels ≥2×ULN ; 6) creatinine clearance of more than 70 ml per minute ; 7) no evidence of hepatocellular carcinoma or liver cirrhosis based on the clinical criteria, ultrasound, and CT examination.

Exclusion criteria included any of the following : 1) coinfection with HCV, HDV, or HIV ; 2) comorbidities with alcoholic or nonalcoholic fatty, drug-induced, or autoimmune liver disease ; 3) serum creatinine >1.5mg/dl ; 4) reluctance to cooperate. The patients were randomly divided into two groups : the ETV group contained 15 patients who were treated orally with 1.0 mg/day ETV, the LAM+ADV group contained 15 patients treated orally with 100 mg/day LAM and 10 mg/day ADV. The study protocol was approved by the ethics committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine.

*Surveillance indicators*

Serum HBV DNA, ALT, HBsAg and HBsAb levels at 0, 12, 24, 36, and 48 weeks were assessed by enzyme-linked immunosorbent assay. Adverse drug reaction: routine blood examination, renal function, and creatine kinase were also evaluated in the course of treatment.

*Statistical analysis*

Categorical variables were defined as a proportion (%) and were compared by $\chi^2$ test. Continuous variables were shown as mean ± standard error and tested with the unpaired Student's *t* test. The Cox proportional hazards model was used to identify the variables determining the clinical endpoint events. All statistical analyses were performed with SPSS 19.0 for windows (IBM Inc., Armonk, NY, USA). A P-value of less than 0.05 was considered significant.

## Results

*Baseline characteristics*

The baseline characteristics of patients including age, sex, baseline levels of HBV DNA, family history of hepatitis B, and history of smoking or ALT were not significantly different between the LAM+ADV and ETV groups in this study (Table 1).

*Rate of undetectable HBV DNA, ALT normalization and HBsAg/HBsAb seroconversion*

Of the 15 patients in the LAM+ADV group, all patients achieved undetectable HBV DNA and ALT normalization at week 48. Of the 15 cases in the ETV group, 11 patients achieved undetectable HBV DNA, and all patients achieved ALT normalization. In terms of HBsAg/HBsAb seroconversion, 3 patients achieved HBsAg/HBsAb seroconversion in the LAM+ADV group, while only 1 patient achieved HBsAg/HBsAb seroconversion in the ETV group (Table 2).

*Virologic breakthrough*

Virologic breakthrough was observed in 4 patients in the ETV group at week 48. No virologic breakthrough was observed in the LAM+ADV group (Table 2).

*Outcome events analysis: multivariate analysis using the Cox proportional hazards model*

The Cox proportional hazards model was used for prediction of undetected viral loads in which age, sex, smoking history, baseline ALT, baseline levels of HBV DNA, and family history of hepatitis B were evaluated. It was observed that therapy with LAM+ADV or a baseline level of HBV DNA <10 (7) copies/ml were independent predictive factors for an undetectable HBV DNA rate in

Table 1. — **Baseline characteristics of patients**

| Variable | LAM+ADV | ETV | P |
|---|---|---|---|
| Age | 40.667±8.756 | 40.733±7.667 | 0.840 |
| Baseline levels of HBV DNA ($10^7$copies/ml) | 2.100±0.839 | 1.802±0.640 | 0.736 |
| ALT (U/L) | 263.667±92.757 | 260.933±107.013 | 0.422 |
| Family history of hepatitis B | 7/15(46.67%) | 10/15(66.67%) | 0.462 |
| History of smoking | 8/15(53.33%) | 3/15(20%) | 0.128 |
| Sex, male | 12/15(80%) | 10/15(66.67%) | 0.628 |

Table 2. — **Rate of undetectable HBV DNA, ALT normalization, HBsAg/HBsAb seroconversion, and virologic breakthrough**

| Classification | LAM+ADV | ETV | χ2 | P |
|---|---|---|---|---|
| Undetectable HBV DNA | 15/15(100%) | 11/15(73.33%) | 4.615 | 0.032 |
| ALT normalization | 15/15(100%) | 15/15(100%) | —— | —— |
| HBsAg/HBsAb seroconversion | 3/15(20%) | 1/15(6.67%) | 1.154 | 0.283 |
| Virologic breakthrough | 0/15 | 4/15(26.67%) | 2.16 | 0.142 |

Table 3. — **Multivariate analysis using the Cox proportional hazards model**

| Variable | RR (95% CI) | P |
|---|---|---|
| Therapy with LAM+ADV *vs* ETV | 2.488(0.956-6.476) | 0.042 |
| Sex (Male *vs.* Female) | 0.885(0.328-2.387) | 0.810 |
| Smoking history (Yes *vs.* No) | 0.977(0.426-2.239) | 0.955 |
| Age (<45 *vs.* ≥45) | 0.710(0.282-1.787) | 0.467 |
| Baseline ALT (<5×ULN *vs.* ≥5×ULN) | 0.809(0.362-1.807) | 0.605 |
| Baseline levels of HBV DNA ($<10^7$ *vs.* $\geq 10^7$) | 0.201(0.045-0.892) | 0.035 |
| Family history of hepatitis B (Yes *vs.* No) | 0.723(0.291-1.795) | 0.285 |

all patients (RR: 2.488, 95% CI: 0.956-6.476, P = 0.042; RR: 0.201, 95% CI: 0.045-0.892, P = 0.035). However, age, sex, smoking history, baseline ALT, or family history of hepatitis B were not significant predictors of an undetectable HBV DNA rate (RR = 0.710, 95% CI: 0.282-1.787, P = 0.467; RR = 0.885, 95% CI: 0.328-2.387, P = 0.810; RR = 0.977, 95% CI: 0.426-2.239, P = 0.955; RR = 0.723, 95% CI: 0.291-1.795, P = 0.285, Table 3).

*Safety and tolerability*

Two patients in the LAM add-on ADV group had transient elevated serum creatinine, but this soon returned to normal. No serious adverse durg reaction occurred in the two groups.

## Discussion

It is widely accepted that antiviral treatment can delay or prevent the progression of chronic hepatitis B (CHB) to cirrhosis and hepatocellular carcinoma and reduce mortality due to CHB-associated complications. Oral antiviral drugs tend to be the first choice for patients with CHB due to advantages such as oral convenience, affordability, and low rate of adverse durg reaction. LAM, the first nucleoside analogue, inhibits HBV DNA polymerase and reverse transcriptase enzymes, rapidly suppressing HBV replication. Although the high-efficiency of LAM was confirmed by many randomized clinical trials, it was also found to induce HBV P-gene mutation leading to drug resistance. It was shown that the drug-resistance rate of oral LAM treatment at 1, 2, 3, 4, and 5 years was 14.7% (4.8%-23.5%), 37.8% (14.3%-65.9%), 49.8% (30.2%-70.5%), 62.0% (52.0%-67.0%), and 70.8%, respectively. Therefore, strategies to rescue patients with LAM treatment failure have become one of the most difficult problems in antiviral therapy for CHB patients.

Adding ADV or switching to other oral antiviral drugs with a high genetic barrier to HBV can effectively inhibit HBV replication following resistance. Kim (6) *et al.* investigated the long-term efficacy of LAM add-on ADV rescue therapy in LAM-resistant CHB and demonstrated that 5-year complete virologic response (CVR, undetectable HBV DNA levels), alanine aminotransferase normalization, and e antigen seroconversion were 86.9%, 92.5%, and 16.7%, respectively. One-year HBV DNA levels were independently associated with CVR. The optimal cut-off level of HBV DNA to predict CVR among patients who failed to achieve CVR at 1 year was 800 IU/ml. During the 5-year treatment, 92.1% of patients with a favorable response (HBV DNA <800 IU/ml at 1-year) achieved CVR. Wang (7) *et al.* compared the cumulative efficacy and resistance of ADV monotherapy and ADV add-on LAM therapy in 100 LAM resistant patients in China. The result showed that after 2 years of treatment, 83.3% of patients who received LAM plus ADV had HBV DNA levels below 1,000 IU/ml, which was more than those who received ADV alone (50%). However, there was no significant difference in serum alanine aminotransferase normalization and e antigen loss/seroconversion.

ETV is currently recommended as a rescue therapy for LAM-resistant HBV infected patients, owing to its high potency in viral suppression and genetic barriers against resistance. Sherman (8) *et al.* conducted a 52-week, double-blind trial of HBeAg positive patients refractory to LAM therapy (persistent viremia or documented YMDD mutations while receiving LAM) and demonstrated that the rate of histologic improvement, composite end points (HBV branched DNA < 0.7 MEq/ml and ALT < 1.25 times the upper limit of normal), and the mean change from baseline in HBV DNA in the ETV-treated group were 55%, 55%, and -5.11 lg copies/ml respectively, which was superior to those of the continuing LAM-sustained treatment group (28%, 4%, and -0.48 lg copies/ml, respectively).

LAM plus ADV combination therapy was more effective and produced longer-lasting effects in treating e antigen-positive CHB patients with LAM resistance than switching to ETV monotherapy. Kim (9) *et al.* observed that after 6 months of rescue therapy for LAM-resistant CHB, the undetectable rate of HBV-DNA using polymerase chain reaction (< 300 copies/ml) and the cumulative HBeAg seroconversion rate in ADV add-on therapy was higher than that of ETV monotherapy. Chung (10) *et al.* demonstrated that the mean reduction in serum HBV DNA levels and achievement of undetectable HBV DNA was significantly less in the ETV group than in the

add-on ADV group at 48 weeks. Multivariate analysis showed that add-on ADV, baseline HBV DNA levels, and the initial virologic response were significant predictors of HBV DNA negativity. Virologic breakthrough was observed in the ETV group but not in the ADV group.

There have been no reports comparing the therapeutic results of LAM add-on ADV or switching to ETV rescue therapy in patients with LAM-resistant e antigen-negative CHB. In this study, we observed that the HBV-DNA undetectability rate (< 500 copies/ml) in the ADV add-on group was higher than in the ETV monotherapy group at 48 weeks, but there was no significant difference in ALT normalization and the HBsAg/HBsAb seroconversion rate between the two groups. Cox analysis showed that therapy with LAM+ADV or baseline levels of HBV DNA <10 (7) copies/ml were independent predictors of HBV DNA negativity in patients. Other factors, such as age, sex, smoking history, baseline ALT, or family history of hepatitis B, were not significant predictors.

However, the present study had some limitations. First, no HBV gene mutation detection was conducted at the beginning of rescue therapy, potentially resulting in patients sensitive to ADV add-on therapy or with a delayed response to LAM treatment being grouped into the ADV add-on group. Second, the enrolled patients were all Chinese and racially East Asian. Differences in drug metabolism or HBV gene subtypes between the Chinese and other Western races may lead to different research results. Third, the follow-up period in this study was terminated at 48 weeks. Whether the result would have changed after a longer follow-up period remains unknown. Finally, the sample size in this study was very small, and further research with larger samples should be conducted. In addition, more high-quality, multi-center, double-blind, randomized controlled clinical trials are required to confirm our findings.

In conclusion, we showed that LAM add-on ADV therapy can suppress HBV replication more effectively than ETV monotherapy at 48 weeks of treatment in patients with HBeAg-negative CHB. No virologic breakthrough was detected in LAM add-on ADV patients. Therapy with LAM+ADV or baseline levels of HBV DNA <10 (7) copies/ml were independent predictive factors for an undetectable HBV DNA rate in patients.

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**Conflict of interest**

The authors declare no conflict of interest.

**Informed consent**

Informed consent was obtained from all individual participants included in the study.

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