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# Lamivudine plus adefovir combination therapy for lamivudine resistance in hepatitis-B-related hepatocellular carcinoma patients

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**Background/Aims:** Lamivudine (LAM) plus adefovir (ADV) combination therapy has been accepted as one of the best treatments for LAM-resistant chronic hepatitis B (CHB). The aim of this study was to determine the efficacy of this combination therapy in hepatocellular carcinoma (HCC) patients.

**Methods:** The medical records of CHB patients who developed LAM resistance and were treated with LAM plus ADV combination therapy for more than 6 months were reviewed. Their virological response (VR; undetectable HBV DNA) and biochemical response (BR; alanine aminotransferase normalization) were evaluated, and the findings of HCC and non-HCC patients were compared.

**Results:** The data from 104 patients (19 with HCC and 85 without HCC) were analyzed. The VR rates did not differ significantly between the HCC and non-HCC groups: 33.3% vs. 55.6% at 12 months ($P$=0.119), 58.3% vs. 67.2% at 24 months ($P$=0.742), 50% vs. 69.8% at 36 months ($P$=0.280), and 66.7% vs. 71.0% at 48 months ($P$=1.000). The BR rates also did not differ significantly between the groups: 55.6% vs. 84.0% at 12 months ($P$=0.021), 58.3% vs. 83.8% at 24 months ($P$=0.057), 70.0% vs. 77.8% at 36 months ($P$=0.687), and 66.7% vs. 80.6% at 48 months ($P$=0.591).

**Conclusions:** The efficacy of LAM plus ADV combination therapy is comparable in HCC and non-HCC patients. **(Clin Mol Hepatol 2013;19:273-279)**

**Keywords:** Chronic hepatitis B; Lamivudine; Adefovir; Resistance; Hepatocellular carcinoma

## INTRODUCTION

A chronic infection with hepatitis B virus (HBV) results in substantial morbidity and mortality worldwide, claiming up to 1 million deaths annually.[1] Chronic hepatitis B (CHB) can be a silent disease for decades, but cirrhosis, liver failure, and hepatocellular carcinoma (HCC) can be the result of untreated infection.[2,3] Lamivudine (LAM) is the first nucleoside analog approved for treatment of CHB, and has been applied globally for CHB patients. But LAM is associated with the highly frequent emergence of drug-resistant mutants, the cumulative rate is about 20% per year.[4,5] LAM and Adefovir (ADV) combination therapy has been accepted as one of the best treatments for LAM resistant CHB patients. The American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Korean Association for the Study of the Liver (KASL) guidelines recommend combination therapy for treatment of LAM resistant CHB patients.[6-8] Lampertico et al reported a virological response of LAM

**Abbreviations:**

AASLD, The American Association for the Study of Liver Disease; ADV, Adefovir; BR, biochemical response; CHB, Chronic hepatitis B; EASL, The European Association for the Study of the Liver; ETV, Entecavir; HBV, hepatitis B virus; HCC, Hepatocellular Carcinoma; KASL, The Korean Association for the Study of the Liver; LAM, Lamivudine; PCR, polymerase chain reaction; RFMP, restriction fragment mass polymorphism; VBT, virological breakthrough; VR, virological response

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resistance patients to combination therapy as 61% at 12 month, 70% at 24 month, 79% at 36 month and 82% at 48 month.[9] Many reports showed that this combination therapy is superior to ADV monotherapy.[10-13] Recently, several Korean reports showed that add-on ADV is superior to a switch to entecavir (ETV).[14-16] However, these previous studies excluded HCC patients. Therefore, data about the efficacy of this combination therapy for HCC patients is limited. The aim of this study was to investigate the efficacy of combination therapy and the predictive factors for a virological response.

## PATIENTS AND METHODS

### Patients

In this study, we retrospectively reviewed the medical records of patients with CHB who developed LAM-resistance and were treated with LAM and ADV combination therapy for more than 6 months. Detection of LAM-resistance was performed by a restriction fragment mass polymorphism (RFMP) method as previously proposed.[17] Patients who received other treatments for LAM-resistance before combination therapy were excluded. Patients started combination therapy before March 2010 and a final follow up was completed March 2012. In cases of liver related death or unrelated death, loss to follow up, liver transplantation, diagnosis of HCC, treatment changes to other protocol, patients were censored. Baseline characteristics were compared based on data at the time just before the combination therapy.

The stage of HCC patients were described according to Barcelona Clinic Liver Cancer (BCLC) classification systems[18] and modified Union for International Cancer Control (UICC)-adopted from Liver Cancer Study Group of Japan.[19]

### Assessment of response

We assessed the response at 3 months, 6 months, 12 months, 24 months, 36 months and 48 months after the combination therapy according to following definitions:

Virological response (VR): undetectable HBV DNA by real time PCR (Cobas Amplicor Taqman PCR, lower limit of detection <300 copies/mL)

Virological Breakthrough (VBT): increase in HBV DNA by >1 $\log_{10}$ copies/ml above the nadir on treatment 2 occasional examination

Biochemical response (BR): alanine aminotransferase (ALT) normalization (≤40 IU/L)

### Statistical analysis

Continuous variables were expressed as median (range) and the categorical variables were expressed as a percentile. Comparisons between groups were performed by Mann-Whitney *U*-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. A *P*-value <0.05 was considered statistically significant. SPSS version 17.0 was used for statistical analysis.

## RESULTS

### Baseline characteristics

A total of 104 patients were analyzed (Non-HCC 85, HCC 19 patients). Males were 66 (63.5%), and the median age was 48.5 years. The baseline median HBV DNA level was 7.3 $\log_{10}$ copies/mL, and HBeAg was positive in 65 patients (62.5%). The median duration of the LAM treatment and combination treatment was 23.0 months and 35.2 months. The HCC group showed a higher incidence of over 50 age patients (78.9% vs. 34.1%, *P*<0.001), a higher incidence of cirrhosis (100% vs. 35.3%, *P*<0.001). In the HCC group, one patient treated with radiofrequency ablation (RFA) and one patient had performed operation. Nine patients were treated with a combination of transarterial chemoembolization (TACE) and RFA or percutaneous ethanol injection (PEI). The other 8 patients were treated with TACE alone (Table 1).

### Response rates

The median HBV DNA level during treatment was not different between the two groups and the median reduction of the HBV DNA level from baseline were also not different except at 12 months (*P*=0.042) (Table 2, Fig. 1).

VR rates during treatment were not different between groups. The BR rates during treatment were also not different except at 12 months (*P*=0.021) (Table 3, Fig. 1). VBT was not observed.

### Clinical courses of patients

Among HCC patients, 7 patients died and one case was related to HCC progression. Liver related deaths other than HCC were 3


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**Table 1.** Baseline characteristics of the subjects

| Variables | Total (n=104) | Non-HCC (n=85) | HCC (n=19) | *P*-value |
|---|---|---|---|---|
| Male | 66 (63.5%) | 52 (61.2%) | 14 (73.7%) | 0.431 |
| Age (yr)* | | | | <0.001 |
| ≤50 | 60 (57.7%) | 56 (65.9%) | 4 (21.1%) | |
| >50 | 44 (42.3%) | 29 (34.1%) | 15 (78.9%) | |
| Cirrhosis | 49 (47.1%) | 30 (35.3%) | 19 (100%) | <0.001 |
| HCC | 19 (18.3%) | | 19 (100%) | |
| HBeAg positive | 65 (62.5%) | 56 (61.2%) | 9 (47.4%) | 0.189 |
| HBV DNA ($log_{10}$ copies/mL)* | 7.3 (4.8-9.0) | 7.3 (4.8-9.0) | 7.1 (5.1-8.0) | 0.520 |
| ALT (IU/L)* | 79 (20-1840) | 86 (20-1840) | 55 (26-816) | 0.161 |
| Child-Pugh score | | | | 0.152 |
| A | 100 (96.2%) | 83 (97.6%) | 17 (89.5%) | |
| B | 4 (3.8%) | 2 (2.4%) | 2 (10.5%) | |
| LAM resistance mutation | | | | 0.337 |
| M204I | 45 (43.3%) | 33 (38.8%) | 12 (63.2%) | |
| M204V+L180M | 22 (21.2%) | 17 (20.0%) | 5 (26.3%) | |
| M204I+L180M | 23 (22.1%) | 22 (25.9%) | 1 (5.3%) | |
| M204V/I+L180M | 9 (8.7%) | 8 (9.4%) | 1 (5.3%) | |
| M204V | 2 (1.9%) | 2 (2.4%) | 0 (0%) | |
| M204V/I | 2 (1.9%) | 2 (2.4%) | 0 (0%) | |
| L180M | 1 (1.0%) | 1 (1.2%) | 0 (0%) | |
| Duration of LAM (mon)* | 23.0 (3-107) | 23.5 (3-107) | 23.0 (6-40) | 0.334 |
| Duration of combination treatment (mon)* | 35.2 (5-63) | 35.5 (5-63) | 29.6 (8-62) | 0.570 |
| BCLC | | | | |
| 0 | | | 4 (21.1%) | |
| A | | | 9 (47.4%) | |
| B | | | 6 (31.6%) | |
| Modified UICC | | | | |
| I | | | 7 (36.8%) | |
| II | | | 7 (36.8%) | |
| III | | | 5 (26.3%) | |
| First line HCC therapy | | | | |
| RFA | | | 1 (5.3%) | |
| Operation | | | 1 (5.3%) | |
| TACE+RFA (or PEI) | | | 9 (47.4%) | |
| TACE | | | 8 (42.1%) | |

HBV, hepatitis B virus; ALT, alanine aminotransferase; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; LAM, lamivudine; BCLC, Barcelona Clinic Liver Cancer; UICC, Union for International Cancer Control; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection.
*Median (range).

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**Table 2.** Change in HBV DNA during combination therapy

| Time | Median HBV DNA ($log_{10}$ copies/mL) | | Median reduction of HBV DNA ($log_{10}$ copies/mL) | |
|---|---|---|---|---|
| | Non-HCC | HCC | Non-HCC | HCC |
| Pre-combination | 7.3 (4.8-8.9) | 7.2 (5.2-8.1) | | |
| 0 mon | 7.3 (4.8-9.0) | 7.1 (5.1-8.0) | | |
| 3 mon | 4.0 (0-7.7) | 4.5 (2.5-5.9) | 2.9 (-2.1-5.8) | 2.8 (-0.1-4.6) |
| 6 mon | 2.7 (0-7.7) | 3.8 (2.5-7.9) | 3.4 (-0.4-7.6) | 2.9 (-0.3-5.1) |
| 12 mon | 2.5 (0-5.7) | 3.3 (2.1-4.5) | 4.1 (1.5-8.1) | 3.3 (1.6-5.1) |
| 18 mon | 2.5 (0-5.6) | 2.7 (0-5.2) | 4.7 (2.0-8.8) | 4.0 (1.4-7.1) |
| 24 mon | 2.1 (0-5.0) | 2.5 (0-4.2) | 5.2 (2.1-8.9) | 4.1 (2.4-7.3) |
| 30 mon | 2.1 (0-5.0) | 2.1 (0-4.0) | 5.2 (0.9-8.9) | 4.4 (1.4-7.6) |
| 36 mon | 2.1 (0-4.0) | 2.1 (0-4.0) | 5.5 (2.0-8.8) | 4.8 (2.2-7.6) |
| 42 mon | 2.1 (0-4.0) | 2.1 (0-4.0) | 5.8 (2.0-9.0) | 5.4 (2.6-7.6) |
| 48 mon | 2.1 (0-4.0) | 2.1 (0-3.0) | 5.8 (2.0-8.3) | 4.4 (3.0-7.6) |

Median (confidence interval).
HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

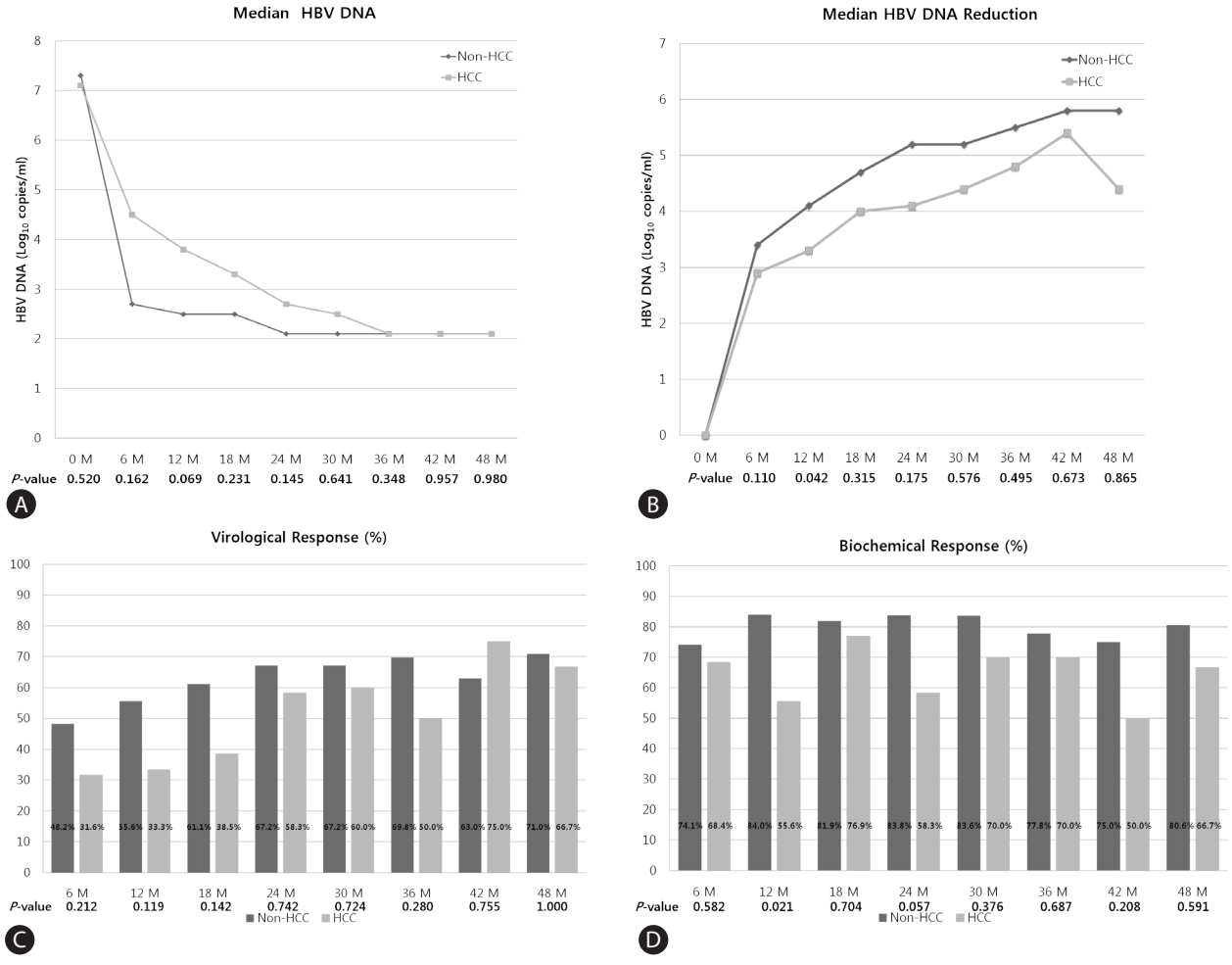


**Figure 1.** The efficacy of combination therapy. (A) Median HBV DNA level. (B) Median reduction in HBV DNA. (C) VR rate. (D) BR rate.


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**Table 3.** The treatment response to combination therapy

| Time | Virologic Response | | | Biochemical Response | | |
|---|---|---|---|---|---|---|
| | Non-HCC | HCC | *P*-value | Non-HCC | HCC | *P*-value |
| 3 mon | 24/80 (30.0%) | 4/18 (30.0%) | 0.578 | 43/80 (53.8%) | 10/18 (55.6%) | 1.000 |
| 6 mon | 41/85 (48.2%) | 6/19 (31.6%) | 0.212 | 63/85 (74.1%) | 13/19 (68.4%) | 0.582 |
| 12 mon | 45/81 (55.6%) | 6/18 (33.3%) | 0.119 | 68/81 (84.0%) | 10/18 (55.6%) | 0.021 |
| 18 mon | 44/72 (61.1%) | 5/13 (38.5%) | 0.142 | 59/72 (81.9%) | 10/13 (76.9%) | 0.704 |
| 24 mon | 45/67 (67.2%) | 7/12 (58.3%) | 0.742 | 57/68 (83.8%) | 7/12 (58.3%) | 0.057 |
| 30 mon | 41/61 (67.2%) | 6/10 (60.0%) | 0.724 | 51/61 (83.6%) | 7/10 (70.0%) | 0.376 |
| 36 mon | 37/53 (69.8%) | 5/10 (50.0%) | 0.280 | 42/54 (77.8%) | 7/10 (70.0%) | 0.687 |
| 42 mon | 26/36 (63.0%) | 6/8 (75.0%) | 0.755 | 30/40 (75.0%) | 4/8 (50.0%) | 0.208 |
| 48 mon | 22/31 (71.0%) | 4/6 (66.7%) | 1.000 | 25/31 (80.6%) | 4/6 (66.7%) | 0.591 |

HCC, hepatocellular carcinoma.

cases (varix bleeding, hepatorenal syndrome, hepatic failure). Two patients died due to cardiac problems and one case was due to pneumonia. There were 4 non-response (NR, decline in the HBV DNA less than 2 $\log_{10}$ copies/mL after 6 month therapy) patients in the HCC group. One patient switched to ETV-ADV combination therapy at 9 months and one patient switched to LAM-tenofovir (TDF) combination therapy at 15 months. The other 2 patients continued the LAM-ADV combination and achieved VR at 12 months and 42 months. Among 9 patients with suboptimal response (SR, decline in the HBV DNA more than 2 $\log_{10}$ copies/mL after 6 month therapy but detectable HBV DNA), 5 patients died and 3 patients achieved VR. One other patient continues combination therapy without VR.

Among non-HCC group, 3 patients were diagnosed with HCC during treatment. These patients already achieved VR before a diagnosis of HCC, and two of them were cirrhotic patients. Two patients were treated with TACE-RFA combination, one patient was treated with RFA alone. Among these, the one patient treated with TACE-RFA combination died due to hepatic failure caused by HCC progression. Among the 8 patients with NR, 2 patients switched to the ETV-ADV combination and 2 patients were lost to follow up. The other 4 patients continued LAM-ADV combination but did not achieve VR. There were 36 patients with SR, and 5 patients among these were lost to follow up, 2 patients switched to LAM-TDF combination, 3 patients switched to ETV-ADV combination and 1 patient stopped treatment due to pregnancy. The other 25 patients continued LAM-ADV combination and 13 patients among them achieved VR.

## DISCUSSION

HBV infection is the one of the most common causes of the liver disease in Korea. Although the prevalence of chronic HBV infection is decreasing, it is still a major etiology of liver cirrhosis and HCC in Korea.[20] LAM was used as a primary treatment for CHB patients before ETV and clevudine became available in Korea in 2007. Therefore, there are many patients who are still treated with LAM and some of them experience LAM resistance.

Many studies have suggested that LAM-ADV combination is superior to ADV monotherapy for the management of LAM resistant CHB patients. Fung et al[10] revealed that patients with ADV resistance were more likely to have been switched from LAM to ADV monotherapy. Rapti et al[11] studied the efficacy of ADV treatment in 42 HBeAg negative patients with CHB who had developed genotypical LAM resistance. The ADV resistance mutations occurred in 21% on ADV monotherapy 15 to 18 months from the start of treatment. Ijaz et al[12] reported that combination therapy resulted in greater viraemia reduction than ADV monotherapy and no ADV-resistance developed during combination therapy. Vassiliadis et al[13] also concluded that adding ADV to LAM is more effective than switching to ADV monotherapy in LAM resistant patients with HBeAg negative CHB. On the other hand, it is also accepted that LAM-ADV combination is superior to ETV monotherapy. Ryu et al[14] compared ADV add-on LAM versus switching to ETV in 92 LAM resistant patients. The mean reduction from the baseline HBV DNA level was greater in the combination group at 12 months. Kim et al[15] compared the cumulative efficacy and resistance of ETV monotherapy, ADV monotherapy and ADV add-on LAM combination therapy. After 6 month of rescue treatment, ADV add-on treatment suppressed HBV replication more effectively than ETV

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or ADV monotherapy. Additionally, no genotypic resistance was detected in the ADV add-on group.

The treatment strategies for LAM resistance are similar between AASLD guideline, EASL guideline. AASLD suggest LAM-ADV combination or LAM-TDF combination, and ETV monotherapy is not recommended.[6] EASL also recommend a switch to TDF or add ADV.[7] However, the long term follow-up data of this combination therapy is not enough. As previously described, Lampertico et al[9] reported follow-up data of 145 LAM resistant patients with CHB who treated LAM-ADV combination up to 4 years.[9] More recently, Shakado et al[21] reported a result of 110 patients who received LAM for more than 12 months and 36 patients among these developed LAM resistance and received with ADV add-on treatment. The VR rates of this study were 47.2% at 1 year, 68.4% at 2 year and 90.9% at 3 year.[21] Inoue et al[22] reported 28 patients who received combination therapy and VR rates were 55.6% at 12 months, 80.0% at 24 months, 86.4% at 36 months, 92.3% at 48 months and 85.7% at 60 months. Korean patient data are limited to 1-2 year follow-up periods.[14-16]

All aforementioned studies excluded HCC patients. The LAM treatment was beneficial in patients with HBV-related HCC and its antiviral effect was comparable to that in CHB patients without HCC, it improved liver function and increased overall survival and tumor-free survival after curative surgery or RFA.[23-26] Jin et al[27] showed that first-line ETV monotherapy is comparably effective in CHB patients with and without HCC. However, there are no data of LMV-ADV for HBV related HCC patients, and the present study is the first report on our knowledge. In the current study, the VR rate and BR rate were comparable between the HCC group and the non-HCC group. Although median reduction of HBV DNA and BR rate at 12 months were lower in HCC group, this difference became insignificant after then. If we consider HCC patients were in advanced stage of liver disease and this lead to reduced immunity and poor general condition, it can be acceptable results. Furthermore, some of HCC patients were under treatment for HCC treatment such as TACE and this can be cause of elevated transaminase.

Three patients of Non-HCC group were diagnosed with HCC during treatment. All of them were in a VR state before HCC diagnosis and 2 of them were cirrhotic patients. Papatheodoridis et al showed that long-term nucleos(t)ide analogue therapy did not eliminate HCC risk and patients with cirrhosis had a high risk of HCC.[28] Furthermore, it is well known that LAM resistance increase the risk of disease progression more than the wild type.[29] Therefore, HCC surveillance has to be continued even when VR is achieved.

In conclusion, LAM and ADV combination therapy is an effective and safe treatment for LAM-resistant CHB patients irrespective of HCC. Although the treatment response is good, the needs of HCC surveillance are not diminished.

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## Conflicts of Interest

The authors have no conflicts to disclose.

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