Short-term overlap lamivudine treatment with adefovir dipivoxil in patients with lamivudine-resistant chronic hepatitis B

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Abstract

AIM: To evaluate the efficacy of short-term overlap lamivudine therapy with adefovir in patients with lamivudine-resistant and naïve chronic hepatitis B, we compared patients receiving overlap therapy with those receiving adefovir alone.

METHODS: Eighty patients who had received lamivudine treatment for various periods and had a lamivudine-resistant liver function abnormality were enrolled. Forty of these patients received adefovir treatment combined with lamivudine treatment for ≥ 2 mo, while the other 40 received adefovir alone. We assessed the levels of hepatitis B virus (HBV) DNA at 0, 12 and 48 wk and serum alanine aminotransferase (ALT) levels after 0, 12, 24 and 48 wk of adefovir treatment in each group.

RESULTS: We found serum ALT became normalized in 72 (87.5%) of the 80 patients, and HBV DNA decreased by ≥ 2 log₁₀ copies/mL in 60 (75%) of the 80 patients at the end of a 48-wk treatment. HBV DNA levels were not significantly different between the groups. The improvements in serum ALT were also not significantly different between the two groups.

CONCLUSION: These findings suggest short-term overlap lamivudine treatment results in no better virological and biological outcomes than non-overlap adefovir monotherapy.

INTRODUCTION

Hepatitis B virus (HBV) infection is the main cause of various liver diseases, such as acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma^[1,2]. To prevent progression into end stage liver diseases, effective and reliable treatment of chronic hepatitis B has been urgently needed. Five regimens have been used for the treatment of chronic hepatitis B. The approved drugs are interferon (conventional and pegylated), lamivudine, adefovir dipivoxil and entecavir. Lamivudine has been effective and tolerable in chronic hepatitis B, but grave drug-resistant mutations developed up to 65% after 5 years of treatment^[3]. Unlike conventional interferon, pegylated interferon treatment could lead to similar or more efficient virological responses than lamivudine, but unwillingness to injection and a number of side effects have prevented its further active usage. However, recent reports showed more optimizing results than ever^[4].

Adefovir dipivoxil is a nucleotide analogue which has been shown to have potent anti-viral activity and side effects similar to those of lamivudine. It also has anti-viral effects against both naïve and lamivudine-resistant cases^[5,6]. Because of provisions in Korean national medical insurance which restrict the use of adefovir to 'rescue' treatment in cases of lamivudine resistance, adefovir dipivoxil is generally prescribed to patients with lamivudine-resistant HBV in Korea^[7,8].

Peter *et al*^[9] suggested the biological and virologic responses were comparable between combinations and adefovir monotherapy in patients with lamivudine-resistant HBV. However, aggravation of hepatitis is more common in patients receiving adefovir monotherapy. Therefore, an overlap period of 2-3 mo was recommended due to the risk of aggravation of liver function during the transition time.

We analyzed the differences between short-term overlap therapy with lamivudine and adefovir and adefovir monotherapy based on viral and blood chemical studies to elucidate the effectiveness of overlap.

MATERIALS AND METHODS

Clinical characteristics of the patients

From March 2004 to May 2006, 80 chronic hepatitis B patients were sequentially enrolled from admission and/or outpatient department and/or the Daejeon St. Mary's Hospital in the Medical College of the Catholic University of Korea. All patients gave written informed consent to participate in this study. All patients had been prescribed lamivudine for chronic hepatitis B and had developed lamivudine-resistant YMDD mutant HBV. YMDD mutation was confirmed by polymerase chain reaction (PCR) in our clinical pathology department. Prior to enrollment, all patients had a serum HBV DNA concentration above 10^5 copies/mL and elevated serum ALT above 80 IU/L. The exclusion criteria were as follows: Patients showing serologic and/or radiological evidence of alcoholic hepatitis or cirrhosis; patients who did not comply with a regular check up of serological and/or virological markers; patients with drug histories, such as herb medications.

Patients received 10 mg adefovir dipivoxil (HepseraTM) orally once a day after enrollment, for 48 wk. Forty patients also received 100 mg lamivudine (ZeffixTM) for 2 mo.

Virological and chemical assays

Serum ALT levels were assessed at intervals of 3 mo and HBV DNA levels were also assessed at 0, 24 and 48 wk. HBeAg and anti-HBe (HBeKit, Beijing North Institute of Biological Technology, Beijing, China) (Quantum Cobra Series II, Packard Inst. Co. Meriden, CT, USA) were assayed at 0, 12 and 48 wk. Serum HBV DNA was examined using an HBV DNA PCR instrument (Covas AmplicorTM, Roche Diagnostics systems, Mannheim, Germany).

Statistical analysis

Data were recorded as mean $\pm$ SD and analyzed by paired *t*-tests. A *P* value of < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of patients

The baseline characteristics of the enrolled patients are shown in Table 1. There were no significant differences in clinical, virological and chemical characteristics between the groups. All enrolled patients completed the 48-wk adefovir treatment schedule.

Table 1 Baseline characteristics of patients in each group

	Overlap	Non-overlap
Age (yr)	43.3 $\pm$ 8.9	43.7 $\pm$ 13.0
Male/female ratio	32/8	29/11
Baseline ALT (IU/L)	188.4 $\pm$ 74.1	209.6 $\pm$ 130.6
Baseline HBV DNA (log ₁₀ copy/mL)	6.9 $\pm$ 0.6	6.9 $\pm$ 0.7
Median lamivudine treatment (mo)	21.5	20.3
HBeAg positive/negative	22/18	25/15

Table 2 Comparison of mean serum ALT levels in each group

	wk after adefovir treatment (IU/L)				
	0	12	24	36	48
Overlap	188.4 $\pm$ 74.1	77.3 $\pm$ 53.9	78.3 $\pm$ 90.2	34.2 $\pm$ 13.4	25.9 $\pm$ 9.9
Non-overlap	209.6 $\pm$ 130.6	78.9 $\pm$ 40.8	43.6 $\pm$ 24.9	34.2 $\pm$ 8.7	24.0 $\pm$ 8.7
<i>P</i> -value	NS	NS	NS	NS	NS

NS: Not statistically significant.

Table 3 Comparison of median serum HBV DNA levels in each group

	wk after adefovir treatment (Log ₁₀ copies/mL)		
	0	12	48
Overlap	6.9 $\pm$ 0.6	5.5 $\pm$ 1.4	3.8 $\pm$ 1.0
Non-overlap	6.9 $\pm$ 0.7	4.2 $\pm$ 1.2	3.4 $\pm$ 1.4
<i>P</i> -value	NS	NS	NS

NS: Not statistically significant.

Comparison of ALT and HBV DNA levels between overlap and non-overlap

At the end of the study schedule, serum ALT level was normalized in 72 (87.5%) of the 80 patients. Overall, the HBV DNA level was decreased by more than 2 log₁₀ copies/mL in 60 (75%) of the 80 patients. HBeAg became negative in 6 (12.7%) of the 47 baseline HBeAg-positive patients. HBeAb seroconversion developed in none of the baseline HBeAg-positive patients.

Serum ALT levels at intervals of 3 mo showed no statistically significant difference between the groups, and ALT level flare up after adefovir monotherapy was seen in only 4 (10%) of the non-overlap patients (*vs* 7.5% of the overlap patients) (Table 2). HBV DNA levels at noted schedules also showed no specific statistically significant difference between the groups (Table 3).

DISCUSSION

There are many suggestions and debates about the management of patients with lamivudine-resistant mutant HBV. However, no obvious consensus has emerged so far. Due to the reported high resistance to lamivudine treatment, many patients who received lamivudine as a therapy for chronic hepatitis B in Korea have had their prescription changed to other anti-viral agents, especially adefovir^[7]. Adefovir has a similar potency and side effects,

but is associated with lower resistance than lamivudine^[5,6]. Whether lamivudine should be prescribed for short-term treatments in combination with adefovir has been a matter of controversy^[9,10]. Thus, we performed a prospective study to elucidate the efficacy of a short-term overlap lamivudine treatment. Although a short-term overlap lamivudine therapy was recommended due to the acute flare ups in serum ALT level reported by Peter *et al*^[9], similar ALT levels were seen in the two groups in our study.

All patients enrolled in our study had compensated chronic liver diseases and no patients had decompensated liver functions after a 48-wk follow up. HBV DNA levels and serum ALT levels were decreased sequentially by adefovir treatment with or without short-term overlap. Therefore, adefovir dipivoxil treatment was effective against lamivudine-resistant chronic hepatitis B.

Hadziyannis *et al*^[11] recently reported adefovir monotherapy for HBeAg-negative chronic hepatitis B for up to 5 years was well tolerated, increasing improvement in the fibrosis of the liver, durable suppression of HBV DNA, and up to 29% resistance. Because of good results following long-term therapy with adefovir with or without short-term overlap lamivudine treatment, adefovir monotherapy without overlap lamivudine therapy might be validated.

Recently, Liu *et al*^[12] reported that an overlap of lamivudine and adefovir treatments for more than 2 mo leads to better virological but not biochemical outcomes in patients with lamivudine-resistant HBV than adefovir treatment alone. However, their study population was smaller than ours and comprised non-randomized cases. Our data showed short-term overlap lamivudine therapy was not superior to non-overlap adefovir monotherapy group with regard to virological and/or biochemical laboratory data. HBeAg loss and HBeAg seroconversion rates were similar to those reported in previous studies by Locarinni *et al*^[13]. Both HBeAg loss and HBeAg seroconversion were no better than lamivudine.

Akyildiz *et al*^[14] also recently reported there was no significant difference between patients with lamivudine resistant chronic hepatitis B treated with adefovir alone and those treated with adefovir in combination with lamivudine for three mo. Therefore, the authors asserted it was not necessary to continue lamivudine treatment while switching to adefovir dipivoxil monotherapy. These results are consistent with ours, although it is not perfectly obvious to assert that switching to adefovir dipivoxil monotherapy with an instant cessation of lamivudine. Our study also has several limitations, such as an insufficient study population and/or non-randomized with blinded state. Moreover, follow up longer than 48 wk is ongoing state.

In summary, our results suggest there is no greater benefit of short-term overlap lamivudine treatment than non-overlap adefovir monotherapy. An overlap of more than 2 mo showed no better virological and/or biochemical results. Therefore, starting adefovir monotherapy immediately instead of applying a short-term overlap might be an efficient choice in cases of lamivudine-resistant HBV. Furthermore, new anti-viral agents with higher potency, durability and/or HBV seroconversion rate should be devised in the near future.

COMMENTS

Background

To prevent progression into end-stage liver diseases, effective and reliable treatment for chronic hepatitis B has been urgently needed. Adefovir dipivoxil is effective in patients with lamivudine-resistant and naïve chronic hepatitis B. The efficacy of short-term overlap treatment with lamivudine and adefovir is not well known. We compared patients who received short-term overlap therapy with those who received adefovir only to evaluate the efficacy of short-term overlap lamivudine therapy.

Research frontiers

Peter *et al* suggested the biological and virologic responses were comparable between combinations of adefovir and lamivudine therapies and adefovir monotherapy in patients with lamivudine-resistant Hepatitis B virus (HBV). However, aggravation of hepatitis was more common in patients receiving adefovir monotherapy. Therefore, an overlap period of 2-3 mo was recommended due to the risk of aggravation of liver function during the transition time. Liu *et al* reported an overlap of lamivudine and adefovir for longer than 2 mo leads to better virological but not biochemical outcomes in patients receiving adefovir for lamivudine-resistant HBV. Akyildiz *et al* reported there was no significant difference between patients with lamivudine-resistant chronic hepatitis B receiving adefovir alone and those receiving adefovir in combination with lamivudine for three months. Therefore, the authors asserted it was not necessary to continue lamivudine treatment while switching to adefovir dipivoxil monotherapy.

Innovations and breakthroughs

Our study has a larger study population and a more objective differentiation of liver function than other studies. However, our study also has several limitations, such as an insufficient study population and/or non-randomized with blinded state.

Applications

There are needs for longer and larger scales of study in this field. Although the recent article from Hadziyannis *et al* showed the superiority of combination therapy, more studies are needed to study the comparison between switching with or without overlap and combination therapy of adefovir and lamivudine.

Terminology

Overlap of lamivudine and adefovir: Use of two regimens at the same time for several months to avoid viral flare up; Switching: When mutant HBV strains resistant to lamivudine develop, other regimens (such as Adefovir, Entecavir and Clevudine) can be substituted for lamivudine.

Peer review

This study evaluates the efficacy of short-term overlap of lamivudine and adefovir in patients with lamivudine-resistant chronic hepatitis B. Compared with non-overlap adefovir monotherapy, short-term overlap lamivudine treatment show no better virological and biological outcomes. This can be interesting for the gastroenterologists and may represent a potentially efficacious approach to the clinical management of acute HBV infection.

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