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Comparison of the Efficacy of Lamivudine and Famciclovir in Asian Patients With Chronic Hepatitis B: Results of 24 Weeks of Therapy

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Lamivudine therapy improves hepatic necroinflammatory activity, decreases progression of fibrosis, and suppresses hepatitis B virus (HBV) replication. Famciclovir has also been shown to have some effect in the suppression of HBV replication. The aim of the study was to compare the effect of treatment with lamivudine and famciclovir on serum HBV DNA levels in patients with chronic hepatitis B and to assess safety. A prospective randomised clinical study was carried out on 100 patients with chronic hepatitis B infection (50 patients received lamivudine 100 mg daily and 50 patients received famciclovir 500 mg three times a day for 12 weeks. From the twelfth week onwards, patients were offered lamivudine 100 mg daily up to 48 weeks). Significantly more patients treated by lamivudine than by famciclovir had undetectable HBV DNA levels after 12 weeks of therapy ($P < 0.001$). The median HBV DNA levels were significantly lower in the lamivudine-treated patients from the second week of treatment onwards ($P < 0.001$ for all time points up to 12 weeks). At week 16, 4 weeks after the famciclovir treated patients were put on lamivudine, there was no longer any difference in HBV DNA levels between the two groups of patients. Both treatments were well tolerated and no serious adverse events were reported. It was concluded that in Chinese patients with chronic hepatitis B infection, lamivudine achieved effective suppression of HBV DNA levels within 4 weeks of therapy whereas famciclovir had a significantly weaker action. ***J. Med. Virol. 67:334–338, 2002.***

KEY WORDS: chronic hepatitis B infection; lamivudine; famciclovir; HBeAg; seroconversion

INTRODUCTION

Hepatitis B virus (HBV) is a considerable health problem with more than 350 million chronic carriers worldwide. It is a major cause of primary liver cancer and cirrhosis [WHO, 1996; Blumberg, 1998]. Effective antiviral therapy is needed urgently.

Lamivudine is an oral nucleoside analogue that inhibits HBV replication. In phase II studies, all lamivudine doses studied (5 to 600 mg/day for up to 6 months) markedly reduced serum HBV DNA in both Asian and Caucasian HBV carriers. With doses of 100 mg per day, the median percent suppression of serum HBV DNA was greater than 98% during treatment in most patients. A 1-year phase III study involving 358 patients showed that when compared with placebo, 100-mg lamivudine daily resulted in significantly better improvement in liver necroinflammatory activity with reduction in the progression of fibrosis, more effective serum HBV DNA suppression, higher rate of hepatitis B e antigen (HBeAg) seroconversion, and more frequent normalisation of serum transaminases [Lai et al., 1998]. However, 14–32% of patients developed genotypic mutations in the YMDD locus that conferred a reduced sensitivity to lamivudine [Lai et al., 1998; Dienstag et al., 1999]. Therefore, combination treatment with other nucleoside analogues may be indicated for longer-term treatment in HBV carriers. Lamivudine has been approved for use in HBV carriers by regulatory authorities in a number of countries.

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Famciclovir, a potent nucleoside analogue against the herpes simplex virus, has been reported to inhibit replication of HBV through inhibition of HBV DNA polymerase [Shaw et al., 1996]. A double-blind dose ranging study of 333 patients showed that with a dose of 500 mg three times daily, serum HBV DNA levels fell to below the limit of detection by the end of 16 weeks of treatment and during subsequent follow-up in 25% of patients [Trepo et al., 1996]. de Man and colleagues [2000] have shown that famciclovir given 500 mg three times a day for 12 months has a significantly higher median decrease (76%) in HBV DNA level compared to that of only 37% in placebo. However, only 13–14% patients had undetectable HBV DNA levels at the end of the treatment.

In vitro studies with duck HBV (DHBV) in primary duck hepatocyte cultures suggest that there is synergistic inhibition of DHBV replication over a wide range of clinically relevant concentrations when lamivudine is combined with penciclovir (the active derivative of famciclovir) [Colledge et al., 1997]. The synergism extends to the persistence of antiviral activity after drug removal and, most encouragingly, to the reduction of the covalently closed circular (ccc) DNA form of DHBV, which is normally very resistant to treatment.

However, the relative potency of lamivudine and famciclovir in chronic hepatitis B patients has not been established. The purpose of this open randomised trial was to compare directly the effect of lamivudine and famciclovir in the suppression of HBV replication in patients with chronic hepatitis B infection.

PATIENTS AND METHODS

Eligible patients included males and females 16 years of age or older with detectable hepatitis B surface (HBsAg) and hepatitis e antigen (HBeAg) in serum at screening and for at least 6 and 3 months, respectively, prior to study entry, detectable HBV DNA levels in serum at screening (Quantiplex Chiron bDNA assay) and raised alanine aminotransferase (ALT) levels $> 1.3 \times$ but $< 10 \times$ the upper limit of normal (ULN) at screening.

Patients were excluded at screening if they had been treated previously with lamivudine or famciclovir, were infected with hepatitis C, hepatitis D or had known HIV co-infection; had any significant history of alcohol ingestion; had decompensated liver disease (serum bilirubin $> 2.5 \times$ upper limit of normal, prothrombin time prolonged > 3 sec, serum albumin outside of the normal reference range, a history of ascites, variceal haemorrhage or hepatic encephalopathy); had evidence of autoimmune hepatitis as indicated by anti-nuclear antibodies titre > 1 in 160, or any serious concurrent medical illnesses that might interfere with therapy.

Patients were not permitted to have received an investigational drug within 30 days of the first dose of study drug and were not permitted to have received any systemic anti-viral therapy, immunomodulators (including interferon), systemic cytotoxic agents, or systemic corticosteroids within 6 months of study screening.

The study was approved by the Ethics Committee of the centre and all patients gave written informed consent before screening. The study was conducted in accordance with the guidelines of the Declaration of Helsinki (1975) and to the principles of Good Clinical Practice.

Patients who fulfilled all entry criteria at a screening visit returned for a baseline assessment within 4 weeks of screening. They were randomised to receive either lamivudine (100 mg daily) or famciclovir (500 mg tds) for 12 weeks (comparative phase). On completion of the comparative phase, all patients were offered treatment with lamivudine on an open label basis until the drug was available on the market.

Patients were seen at weeks 2, 4, 8, and 12 (comparative phase) and weeks 16, 24, 32, 40, and 48 and thereafter at 8 weekly intervals (open label lamivudine phase). At each visit, adverse events were specifically asked for using standard questions and treatment compliance checked. Blood was taken for biochemistry and haematology evaluations. Sera were analysed for HBV DNA at every visit up to week 48 and for HBeAg and HBsAg at screening, baseline, and weeks 12, 24, and 48. This manuscript includes data up to 24 weeks of follow-up.

The primary endpoint was defined as the undetectability of HBV DNA on at least two consecutive HBV DNA measurements taken at least 7 days apart using the assay chosen for this study.

Assay Methodology

Serum HBV DNA was quantified by the Quantiplex bDNA (Chiron Corporation, Emeryville, CA) (lower limit of detection 2.5 pg/mL). HBeAg and antibody to HBeAg (anti-HBe) were assayed by IMX automation and HBsAg and antibody to HBsAg (anti-HBs) were assessed by AxSYM Immunoassay Automation (Abbott Laboratories, Chicago, IL).

Statistical Analysis

The sample size of 100 patients was planned to provide 80% power to detect a statistically significant difference at the 5% level using a 2-sided test between expected response rates of 60% in famciclovir-treated patients and 90% in lamivudine-treated patients on the primary endpoint.

HBV DNA levels between the two groups of patients are compared using the Chi-square test and Fisher's exact test. The comparison includes both the median HBV DNA levels and $\log_{10}$ reduction of HBV DNA. Median HBV DNA levels were analysed using the non-parametric Wilcoxon rank test, with a median treatment difference calculated using the Hodges Lehman estimator. In the analyses of HBeAg, anti-HBe, HBsAg, and anti-HBs, missing data were assigned the values of the last observation. In the analysis of HBV DNA and ALT, missing data were considered as failures, that is, as having detectable HBV DNA or abnormal ALT.

TABLE I. Patient Characteristics at Baseline

	Lamivudine	Famciclovir
Intent-to-treat population	50	50
Median age in years (range)	28 (16–48)	31 (16–54)
% of male:female	70:30	80:20
% of patients with ALT above the upper limit of normal	56	54
Median HBV DNA in pg/mL (range)	3350.0 (5.40–20,000.00)	2700.0 (13.00–20,000.00)
Median ALT in U/L (range)	55.0 (11.00–506.00)	52.5 (12.00–838.00)

RESULTS

The intent to treat population consisted of 100 Chinese patients with chronic hepatitis B, 50 in each treatment group. Baseline characteristics are presented in Table I. There were no clinically relevant differences between the two groups. None of the patients were positive for antibody against HBeAg (anti-HBe). Two patients who received famciclovir were withdrawn before week 2 (see Safety).

HBV DNA Reduction

The median HBV DNA levels of the two groups of patients are shown in Figure 1. The median HBV DNA level of the lamivudine-treated patients became significantly lower than that of the famciclovir-treated patients by week 2 ($P < 0.001$) and remained significantly lower at all time points tested in the 12 weeks of the comparative phase of the trial. This difference in median HBV DNA levels was no longer present 4 weeks after the famciclovir-treated patients were given open label lamivudine. The median HBV DNA level of the lamivudine-treated group fell below the lower limit of detectability of the assay (2.5 pg/ml) by week 4.

The decrease in HBV DNA from the baseline levels in the two groups of patients, expressed as $\log_{10}$ reduction, is shown in Table II. For the lamivudine-treated patients, all had over 0.5 $\log_{10}$ reduction from week 2 onwards. In contrast, only 44% of famciclovir-treated patients had over 0.5 $\log_{10}$ reduction at week 2 and 56% at week 12 ($P < 0.001$ for both time intervals compared with the lamivudine-treated patients). Four weeks after these patients were put on open label lamivudine, all the patients had over 0.5 $\log_{10}$ reduction.

None of the patients treated with lamivudine and 8% of the patients on famciclovir had HBV DNA levels rising above the baseline levels during therapy.

HBeAg Seroconversion and Loss of HBsAg

At week 12, five of the 50 patients treated with lamivudine (10%) and none of the 48 patients treated with famciclovir had HBeAg seroconversion (loss of HBeAg, development of anti-HBe with undetectable HBV DNA). One of these five patients on lamivudine became positive for both HBeAg and anti-HBe at week 24. (The patient had subsequently stable HBeAg seroconversion at week 48.)

Up to week 24, none of the patients lost HBsAg.

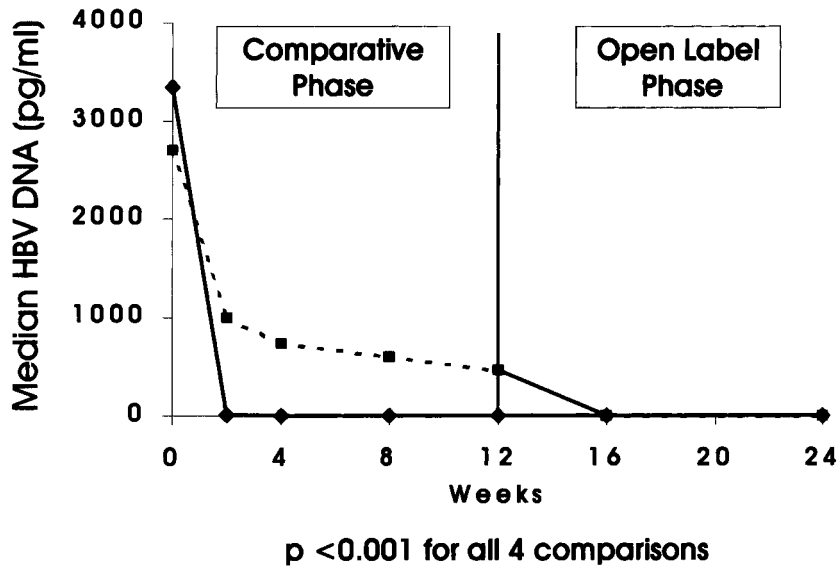

Fig. 1. The median HBV DNA levels in pg/ml of 100 patients on lamivudine and famciclovir for 12 weeks (comparative phase) and on lamivudine for 12 more weeks (open label phase). Continuous line represents the patients on lamivudine; dashed line represents the patients on famciclovir.

TABLE II. Change in HBV DNA Levels From Baseline, Expressed as Log_{10} Reduction, During Treatment

HBV DNA reduction expressed in log_{10}	Lamivudine [n = 50(%)]	Famciclovir [n = 50(%)][a]	*P* value*
Week 2			
< 0.5	0/50	27/48 (56)	$P < 0.001$
≥ 0.5 to < 2.0	19/50 (38)	20/48 (41)	
≥ 2.0	31/50 (62)	1/48 (2)	
Week 4			
< 0.5	0/50	25/48 (52)	$P < 0.001$
> 0.5 to < 2.0	9/50 (18)	20/48 (42)	
≥ 2.0	41/50 (82)	3/48 (6)	
Week 8			
< 0.5	0/50	18/48 (38)	$P < 0.001$
> 0.5 to < 2.0	9/50 (18)	26/48 (54)	
≥ 2.0	41/50 (82)	4/48 (8)	
Week 12 (end of comparative phase)			
< 0.5	0/50	21/48 (44)	$P < 0.001$
> 0.5 to < 2.0	9/50 (18)	23/48 (48)	
≥ 2.0	41/50 (82)	4/48 (8)	
Week 16			
< 0.5	0/50	0/48	
≥ 0.5 to < 2.0	11/50 (22)	9/48 (19)	N.S.
≥ 2.0	39/50 (78)	39/48 (81)	
Week 24			
< 0.5	1/50 (2)	1/48 (2)	
≥ 0.5 to < 2.0	8/50 (16)	8/48 (17)	N.S.
≥ 2.0	41/50 (82)	39/48 (81)	

[a]These patients were put on lamivudine 100 mg daily from week 12 onwards.
*Fisher's exact test. N.S. = not significant.

Alanine Aminotransferase (ALT) Response

Figure 2 shows the median ALT levels of the two groups of patients. Both groups demonstrated a gradual fall in median ALT levels during the first 12 weeks of the study.

However, the proportion of patients with ALT normalisation during the first 12 weeks was significantly greater ($P = 0.04$) in the lamivudine patients group (57%, 16/28) than in the famciclovir patients group (30%, 8/27). This fall continued from week 12 to week 24 when both groups of patients were on lamivudine.

Safety

Two patients treated with famciclovir withdrew before week 2. One withdrew for personal reasons; the second patient withdrew because they experienced

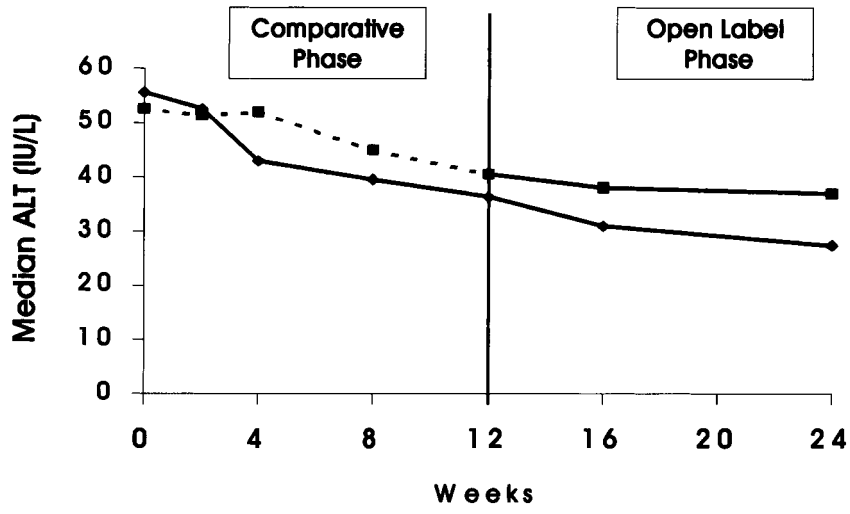

Fig. 2. The median alanine transaminase levels in IU/L of 100 patients on lamivudine and famciclovir for 12 weeks (comparative phase) and on lamivudine for 12 more weeks (open label phase). Continuous line represents the patients on lamivudine; dashed line represents the patients on famciclovir.

TABLE III. Proportion of Patients Experiencing the Most Common Adverse Events (i.e., Reported by > 5% of Patients) During the Comparative Phase of the Study

	Lamivudine	Famciclovir
Number of patients	50	48[a]
Patients with at least one adverse event (%)	52	50
Influenza (%)	22	20
Common cold (%)	14	2
Stomach ache (%)	6	8
Tiredness (%)	2	10
Headache (%)	8	2
Sore throat (%)	2	6

[a]Two patients who were withdrawn from the study before week 2 were excluded from analysis.

a sense of airway obstruction and tiredness after one day of famciclovir.

The most common side-effects (occurring in over 5% of the patients) are listed in Table III. Most of the adverse events were mild and transient, and considered to be unrelated to either drug. Of interest is that five patients treated with famciclovir complained of significant sleepiness and tiredness 1 to 2 hours after taking the morning dose of famciclovir. The duration of sleepiness varied from a few hours to almost the whole day. One patient on lamivudine also complained of tiredness. However, the tiredness had no apparent time relationship to the ingestion of lamivudine.

No serious adverse events were reported.

DISCUSSION

This study is the first trial comparing the effects of two nucleoside analogues, lamivudine and famciclovir, on the suppression of HBV DNA in patients with chronic hepatitis B. It is also the third trial to document the antiviral potency of famciclovir against HBV [Main et al., 1996; Manet et al., 2000].

It was found that while lamivudine was highly effective in the suppression of HBV DNA from the second week onwards, famciclovir was significantly less potent, with 44% of patients having less than 0.5 $\log_{10}$ reduction in HBV DNA even after 12 weeks of treatment on a dosage, which is double that for the treatment of herpes simplex viruses (Fig. 1, Table II). The HBV DNA of the patients on famciclovir responded rapidly when they were switched to lamivudine. This suggests that the significantly less effective suppression of HBV DNA in the famciclovir-treated patients was not related to the patients nor to the viral load but the relatively weak action of famciclovir on HBV.

The specific action of famciclovir against the herpes simplex virus is well documented [Vere Hodge, 1993]. The intracellular phosphorylation of the active derivative of famciclovir, penciclovir, is facilitated by a virally encoded deoxynucleoside kinase in herpes simplex virus-infected cells. This process forms preferentially the (S)-enantiomer of penciclovir triphosphate which is a very effective inhibitor of herpes simplex virus DNA polymerase. HBV-infected cells have not been reported to contain any virally encoded substances that can facilitate the action of famciclovir. It is not surprising that the antiviral potency of famciclovir against HBV is much weaker than its action on herpes simplex virus.

It is difficult to ascertain whether the 10% HBeAg seroconversion in the patients receiving lamivudine during the first 12 weeks was due to the effect of lamivudine since, firstly, there was no placebo arm in this study, and, secondly, no other patients had HBeAg seroconversion during the subsequent 12 weeks when all the patients were put on lamivudine.

In conclusion, famciclovir had a significantly weaker action in the suppression of HBV DNA when compared with lamivudine. Even though both compounds are equally safe, famciclovir is probably not an ideal agent for combination therapy with lamivudine in the treatment of chronic hepatitis B, especially since there are newer nucleoside analogues currently being studied that are very potent suppressors of the HBV.

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