

# Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease

Man-Fung Yuen, Wai-Kay Seto, Danny Hoi-Fan Chow, Kit Tsui, Danny Ka-Ho Wong, Vincent Wing-Shun Ngai, Benjamin Chun-Yu Wong, James Fung, John Chi-Hang Yuen and Ching-Lung Lai\*

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

\*Corresponding author: Tel: (852) 28554252; Fax: (852) 287162863; E-mail: hrmelcl@hkucc.hku.hk

**Background:** Long-term effects of lamivudine treatment on chronic hepatitis B patients without advanced disease remain unknown. Our aim was to investigate the effects of long-term lamivudine treatment and lamivudine-resistant virus (YMDD) on the development of cirrhosis and hepatocellular carcinoma (HCC) in asymptomatic patients without advanced disease.

**Methods:** One hundred and forty-two hepatitis B e antigen (HBeAg)-positive patients (median age: 33.9 years) on long-term lamivudine (median treatment duration: 89.9 months) and 124 HBeAg-positive controls (median age: 33.4 years) were prospectively followed up. Patients were monitored for the development of cirrhosis and HCC, liver biochemistry, hepatitis B virus (HBV) DNA levels, HBeAg seroconversion and hepatitis flares. YMDD mutations (YMDD-MT) were determined annually.

**Results:** Lamivudine-treated patients had a significantly lower cumulative rate of development of cirrhosis and/or

HCC compared with controls ( $P=0.005$ ). YMDD-MT occurred in 76.3% of patients after 8 years of lamivudine treatment. When compared with controls and patients with YMDD-MT, patients without YMDD-MT had the greatest reduction of HBV DNA and bilirubin levels, slowest decline of albumin level, highest rate of HBeAg seroconversion and lowest risk of hepatitis flare. Patients with YMDD-MT still had a lower risk for developing cirrhosis and/or HCC ( $P=0.024$ ) and a greater HBV DNA reduction ( $P=0.001$ ) in comparison with controls. Patients with YMDD-MT and controls had a similar chance of hepatitis flares and hepatic decompensation.

**Conclusions:** Long-term lamivudine treatment was associated with a reduced chance of developing cirrhosis and HCC in patients without advanced disease. Although YMDD-MT reduced the benefits from lamivudine therapy, the outcome of these patients was still better than untreated patients.

## Introduction

There is an estimated 350–400 million people with chronic hepatitis B (CHB) infection worldwide, resulting in one million deaths annually [1,2]. Total eradication of the hepatitis B virus (HBV) is seldom achieved by current treatment, especially in Asian patients who usually acquire the disease in early childhood.

The ultimate goal of CHB treatment is the prevention of cirrhosis-related complications and hepatocellular carcinoma (HCC). These can still occur in patients after hepatitis B e antigen (HBeAg) seroconversion and with HBV DNA level  $<10^5$  copies/ml [3,4]. Liaw *et al.* have shown that 3-year lamivudine treatment can retard the progression of cirrhosis and reduce the risk of HCC in patients with advanced disease, including pre-cirrhotic and cirrhotic disease (Ishak's fibrosis score of  $\geq 4$ ) [5]. To date, the beneficial effects of long-term lamivudine treatment in asymptomatic patients without advanced disease has not been investigated. In addition, the

long-term effects of lamivudine-resistant mutations (YMDD mutations; YMDD-MT) beyond 3 years of treatment needs to be explored.

The primary aim of this study was to determine the effect of long-term lamivudine treatment on the risk of developing cirrhosis and HCC in asymptomatic patients without advanced disease and no clinical evidence of cirrhosis. The secondary aim was to determine the long-term effects of YMDD-MT on the disease progression.

## Patients and methods

The present study recruited patients from three previous clinical trials: NUCB 3009 ( $n=88$ ), which was continued as trial NUCB 3018 ( $n=81$ ), and NUCB 4003 ( $n=99$ ), sponsored by Glaxowellcome Research Laboratories between 1 June 1994 and 31 August

1997 [6,7]. Patients in the NUCB 3009 trial had baseline and 1-year protocol-required liver biopsies; none of the patients showed any evidence of cirrhosis at baseline. The three trials were approved by the Institutional Review Board of the University of Hong Kong and were conducted in the Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong. Written informed consent was obtained from all patients. All patients were prospectively followed up; the follow-up study was also approved by the Institutional Review Board. All patients were hepatitis B surface antigen (HBsAg) positive by enzyme-linked immunosorbent assay (ELISA; Abbott Laboratories, Chicago, IL, USA) for at least 6 months and HBeAg positive (ELISA, Abbott Laboratories). To eliminate patients with advanced disease on presentation, those with albumin levels <35 g/l and bilirubin levels >1.5× upper limit of normal (ULN) were excluded. All patients were negative for antibodies against hepatitis C and D and HIV. Patients with >20 g per day of alcohol intake on a regular basis were excluded.

One of our recent studies shows that the age range for the development of complications was between 24 and 83 years (median age: 57 years) [3]. As the aim of the present study was to investigate the effect of lamivudine on the development of cirrhosis and HCC, 20 years was chosen as the cut-off age for patients included in this study. The details of the patients included in this study are shown in Figure 1.

Of the 142 patients recruited, 14 with YMDD-MT were given adefovir dipivoxil in addition to lamivudine. There was no difference in the median peak alanine aminotransferase (ALT) levels between patients with YMDD-MT who received and who did not receive adefovir dipivoxil (182 U/l [range: 99–990 U/l] versus 240 U/l [range: 66–890 U/l], respectively;  $P=0.52$ ). There was also no difference in the percentage of patients with hepatic decompensation (defined below) between patients who received and who did not receive adefovir dipivoxil (7.1% [1/14] versus 8.5% [8/94], respectively;  $P=1.0$ ). The date of adding adefovir dipivoxil was regarded as the last follow up; otherwise, all patients, irrespective of whether they had hepatitis flares with or without YMDD-MT, were maintained continuously on lamivudine 100 mg daily until the time of writing.

As control, we recruited all patients between 20–60 years old who were first seen in the Hepatitis clinic, The University of Hong Kong, Queen Mary Hospital between 1 June 1994 and 31 August 1997. They fulfilled the inclusion criteria listed above, but did not join any of the three trials. The upper age limit of 60 was set because the oldest lamivudine-treated patient was 54.4 years old. A total of 167 patients

were identified. Details of the 124 patients eventually recruited as controls in this study are shown in Figure 1. Of these, 18 patients were initially recruited for the three lamivudine trials (12 declined to join because of personal reasons and six were not eligible because of low HBV DNA levels). The remaining 106 patients had not been recruited for the three trials because the enrollments were already full. There was no bias in deciding which patients were recruited into the three trials and which were not. All control patients had not received lamivudine until the last follow up.

Patients were followed up every 3–6 months. Liver biochemistry,  $\alpha$ -fetoprotein (AFP), and HBV serology including HBsAg, HBeAg and antibody to HBeAg (anti-HBe) (ELISA, Abbott Laboratories) were checked at each follow up. Patients with hepatitis B flares (defined as ALT levels >2×ULN without evidence of other causes of increased ALT levels, such as hepatitis A, C, D and E, steatohepatitis, and alcoholic and drug intake) had more frequent follow-up visits whenever indicated. Hepatic decompensation is defined as prolonged prothrombin time >5 sec and/or increased bilirubin levels >2× ULN.

For lamivudine-treated patients, HBV DNA levels were checked at baseline; year 1, 3, 5 and 8; and last follow up. For control patients, HBV DNA levels were checked at baseline, year 5 and 8, and last follow up. HBV DNA levels were measured by COBAS TaqMan™ HBV test (Roche Diagnostics, Branchburg, NJ, USA) with a lower limit of detection of 35 copies/ml (6.0 IU/ml).

Emergence of YMDD mutants (YMDD-MT) was surveyed annually up to the last follow up for every treated patient. HBV genotypes were also determined. Line probe assays were used to determine the emergence of YMDD-MT and HBV genotypes (INNO-LiPA HBV DR and Genotyping, respectively; Innogenetics NV, Belgium). The methodologies were described in previous studies [8,9].

Patients with albumin levels <35 g/l on follow up were arranged to undergo ultrasound examination. Development of cirrhosis was defined as ultrasonographic evidence of a small-sized liver with or without splenomegaly and ascites [10,11]. Patients were monitored for the development of cirrhosis-related complications including ascites, esophageal varices and hepatic encephalopathy. Screening of HCC were performed by 6 monthly AFP measurement followed by ultrasound and computerized tomography when AFP was increased. HCC were diagnosed either by histology or typical features on imaging.

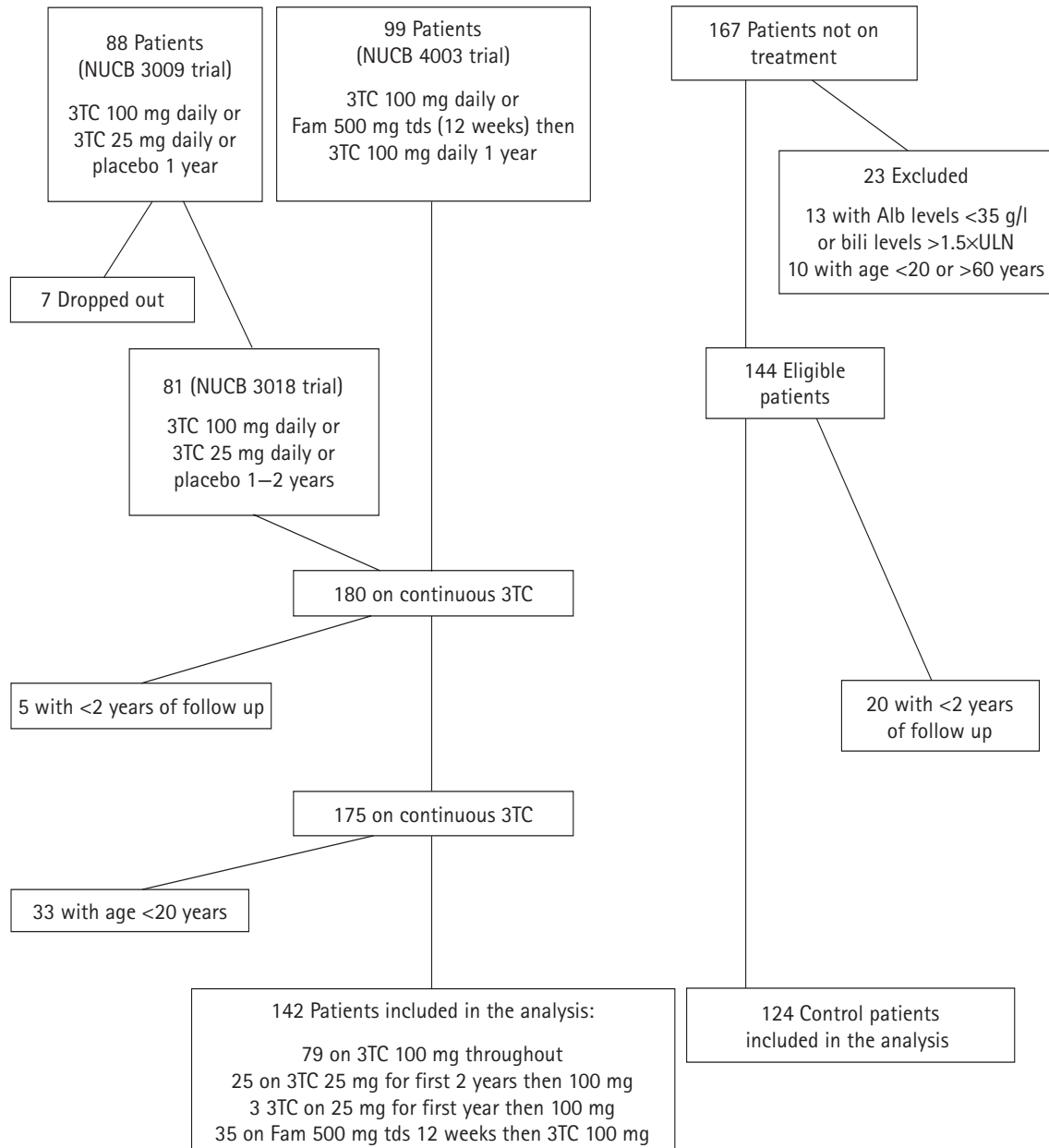
#### Statistical analysis

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 13.0 for

Windows; SPSS Inc., Chicago, IL, USA). Mann–Whitney U test was used for continuous variables with skewed distribution and the  $\chi^2$  test with Yates correction factor or Fisher’s exact test were applied for categorical variables. The Kaplan–Meier method using the Log Rank

test was applied for the cumulative rate of HBeAg seroconversion, hepatitis flare, and development of cirrhosis and HCC. HBV DNA levels below the lower detection limit (<35 copies/ml [6.0 IU/ml]) were recorded as 35 copies/ml (6.0 IU/ml).

Figure 1. Flow of study population



In the NUCB 3009 trial, patients were randomized to receive lamivudine (3TC) 100 mg or 25 mg daily, or placebo for 1 year. They were then rolled over to the NUCB 3018 trial. Patients previously receiving 3TC 100 mg (or 25 mg) daily were either given 3TC 100 mg (or 25 mg) or placebo for 1–2 years, followed by open-label 3TC 100 mg daily at the end of the third year. All patients re-randomized to receive placebo had rebound of hepatitis B virus DNA at around 4 weeks (wks) after receiving placebo. They were given open-label 3TC 100 mg daily. For patients receiving placebo in NUCB 3009 trial, all were given 3TC 100 mg daily. In the NUCB 4009 trial, patients were randomized to receive either 3TC 100 mg daily or famciclovir (Fam) 500 mg three times a day (tds) for 12 weeks followed by open-label 3TC 100 mg daily. Sixteen patients decided to stop 3TC on their own initiatives after 4.2–10.6 years of treatment. Alb, albumin; Bili, bilirubin.

**Table 1.** Baseline demographic data, liver biochemistry, HBV DNA levels and duration of lamivudine treatment and follow-up of the study population

Characteristic	Lamivudine-treated patients (n=142) <sup>†</sup>	Control patients (n=124)
Sex, M:F	106:36	90:34
Age, years	33.9 (20.2–54.4)	33.4 (20.8–59)
Liver biochemistry		
Albumin, g/l (normal 38–48)	46 (37–55)	47 (37–54)
Bilirubin, $\mu$ mol/l (normal 7–19)	10 (3–25 <sup>‡</sup> )	11 (3–27 <sup>‡</sup> )
ALT, U/l	65 (14–838)	56.5 (9–850)
ALT $\leq$ 1 $\times$ ULN, n (%)	50 (35.2%)	49 (39.5%)
ALT $\geq$ 2 $\times$ ULN, n (%)	52 (36.7%)	42 (33.9%)
ALT $\geq$ 5 $\times$ ULN, n (%)	17 (12.0%)	17 (13.7%)
HBV DNA, copies/ml	5.5 $\times$ 10 <sup>8</sup> (17,600–5.3 $\times$ 10 <sup>11</sup> )*	6.5 $\times$ 10 <sup>6</sup> (35–4.0 $\times$ 10 <sup>9</sup> )*
HBV DNA, log	8.7 (4.2–11.7)	6.8 (1.5–9.6)
Number of patients with HBV levels:		
<10 <sup>3</sup>	0 (0%)	3 (2.4%)
$\geq$ 10 <sup>3</sup> –10 <sup>4</sup>	1 (0.7%)	7 (5.6%)
$\geq$ 10 <sup>4</sup> –10 <sup>5</sup>	1 (0.7%)	13 (10.5%)
$\geq$ 10 <sup>5</sup> –10 <sup>6</sup>	5 (3.5%)	26 (21.0%)
$\geq$ 10 <sup>6</sup> –10 <sup>7</sup>	21 (14.8%)	24 (19.4%)
$\geq$ 10 <sup>7</sup> –10 <sup>8</sup>	44 (31.0%)	25 (20.2%)
$\geq$ 10 <sup>8</sup>	70 (49.3%)	26 (21.0%)
Duration of treatment or follow up, months	89.9 (26.5–128.3) <sup>§</sup>	107.8 (30.9–127.3) <sup>¶</sup>

Continuous variables are expressed in median (range). \* $P<0.001$ . <sup>‡</sup>Only 3/70 (4.3%) patients had Ishak fibrosis score of 4 (0 indicates no fibrosis and 6 indicates cirrhosis). <sup>†</sup>One patient in each group had albumin levels of 46 or 47 g/l with normal alanine aminotransferase (ALT) levels. The isolated mild increase in the bilirubin levels was probably due to Gilbert's syndrome. <sup>§</sup>Lamivudine treatment; <sup>¶</sup>follow up. HBV, hepatitis B virus; ULN, upper limit of normal.

## Results

### Baseline demographic data

The baseline data, HBV DNA levels and duration of treatment and follow up of the two groups of patients are listed in Table 1. All patients were positive for HBeAg at baseline. The baseline median HBV DNA level was significantly higher in lamivudine-treated patients compared with control patients.

The distribution of genotypes B and C were: 40 (28.2%) and 102 (71.8%) for lamivudine-treated patients and 31 (25%) and 93 (75%) for controls, respectively.

### Percentage of patients with YMDD-MT

The percentage of patients with YMDD-MT over 8 years of lamivudine treatment is depicted in Figure 2. Overall, 23.7% of the treated patients maintained YMDD wild-type (YMDD-WT) throughout the 8 years.

### Effect of lamivudine therapy on HBV DNA levels, HBeAg seroconversion and biochemical parameters

The median log reduction of HBV DNA levels at year 1, 3, 5 and 8 in the lamivudine-treated patients and at year 5 and 8 in controls are depicted in Figure 3. Lamivudine-treated patients with YMDD-WT displayed significantly greater reduction of HBV DNA than controls and lamivudine-treated patients

with YMDD-MT. Seventeen patients with YMDD-WT, 58 patients with YMDD-MT and 83 control patients were still being followed up at year 8. Ten (58.8%) patients with YMDD-WT had HBV DNA levels <1,000 copies/ml (median value: 171.8 IU/ml) compared with 12 (14.5%) controls ( $P<0.001$ ) and six (10.3%) patients with YMDD-MT ( $P<0.001$ ; no significant difference was found between the latter two groups of patients). Eight lamivudine-treated patients (47.1%) with YMDD-WT compared with three controls (3.6%,  $P<0.001$ ) and two lamivudine-treated patients (3.4%,  $P<0.001$ ) with YMDD-MT had HBV DNA levels below the lower detection limit (<35 copies/ml [6.0 IU/ml]).

The cumulative rates of HBeAg seroconversion and hepatitis flare are illustrated in Figure 3. Patients with YMDD-WT had a significantly higher cumulative rate of HBeAg seroconversion and lower cumulative rate of hepatitis flares compared with patients with YMDD-MT and control patients. There was no difference in the cumulative risk of hepatitis flare (Figure 3,  $P=0.22$ ), or of hepatitis flare resulting in decompensation between lamivudine-treated patients with YMDD-MT and controls (10.1% versus 6.6%, respectively;  $P=0.58$ ). The cumulative rate of HBeAg seroconversion was higher in control patients compared with patients with YMDD-MT.

Two patients aged 21 and 28.3 years receiving lamivudine lost HBsAg and developed antibody against HBsAg (anti-HBs) after 25 and 45.3 months of lamivudine treatment, respectively. One control patient aged 41.4 years lost HBsAg after 38.3 months of follow up.

The changes in albumin and bilirubin levels at year 3, 5 and 8 are listed in Table 2. Compared with controls, lamivudine-treated patients with YMDD-WT had significantly less reduction of albumin levels starting from year 5 onwards and significantly greater reduction of bilirubin levels at year 8.

At year 8, 88.2% (15/17) of lamivudine-treated patients with YMDD-WT had normal ALT levels compared with 57.8% (48/83) of controls ( $P=0.037$ ) and 60.3% (35/58) of lamivudine-treated patients with YMDD-MT ( $P=0.064$ ).

There was no difference in cumulative HBeAg seroconversion rate ( $P=0.33$ ) and YMDD-MT development ( $P=0.42$ ) between lamivudine-treated patients with genotypes B and C.

#### Effect of lamivudine therapy on the development of cirrhosis and HCC

Eight lamivudine-treated patients (one with YMDD-WT and seven with YMDD-MT) and 19 controls developed cirrhosis and/or HCC. Five (62.5%) of the eight lamivudine-treated patients and 12 (63.5%) of the 19 controls were anti-HBe positive at the time of the development of cirrhosis and/or HCC. The cumulative rate of development of cirrhosis and/or HCC is illustrated in Figure 4. The complications that the patients developed were as follows: seven lamivudine-treated patients developed cirrhosis (one with ascites) and one developed HCC; and 19 controls developed cirrhosis (one with ascites and one with oesophageal varices), three of whom also developed HCC. The baseline characteristics of the patients who developed cirrhosis and/or HCC were same as those who did not develop cirrhosis or HCC.

All seven patients with YMDD-MT who developed cirrhosis and/or HCC developed the YMDD-MT within the first 3 years of treatment.

## Discussion

The only other compound licensed for the treatment of CHB with long-term follow-up data is interferon- $\alpha$  (IFN- $\alpha$ ). Whereas most of the studies involving Caucasian patients show that a 16-week course of IFN- $\alpha$  treatment is of continuing beneficial effect in enhancing HBeAg seroconversion, and thus decreasing cirrhotic complications [12–14], the long-term efficacy of IFN- $\alpha$  in Asian patients is more controversial. A study from Taiwan involving 67 treated patients and 34 controls shows that IFN- $\alpha$  treatment induces

borderline improvement in HBeAg seroconversion ( $P=0.049$ ) and has no effect on the development of cirrhosis and cirrhosis-related complications, but it does decrease the development of HCC [15]. This study recruited patients with mean baseline ALT levels  $>220$  U/l. The only other study, with 207 treated patients and 203 controls, shows no beneficial effect in HBeAg seroconversion and, more importantly, no effect on the subsequent development of cirrhosis-related complications and HCC [16]. These complications continue to develop after HBeAg seroconversion, and even after HBsAg seroclearance [17], probably due to the continued viraemia, though at relatively low levels. In the study of Yuen *et al.*, 88% of anti-HBe patients treated by IFN- $\alpha$  had HBV DNA detectable by PCR assay even after HBeAg seroconversion [16].

The present study compared the long-term effects of lamivudine treatment with a control population. One of the limitations of the present study is the possible underestimation of the incidence of early cirrhosis because cirrhosis was defined as the development of small-sized liver, with or without splenomegaly and ascites, by ultrasound criteria. Similarly, the use of AFP level followed by ultrasound to diagnose HCC may have led to a delay in HCC diagnosis. Another study limitation is that the control group was not from the original lamivudine trials. All placebo patients from the original trials were given lamivudine after week 52 according to the trial protocols. For ethical reasons, it was no longer possible to conduct a trial determining the efficacy of long-term nucleoside analogues in CHB patients compared with placebo-controlled patients. The baseline parameters of the lamivudine-treated and control patients in the present study were well matched except that the median baseline HBV DNA level of the controls was 2 logs lower compared with the

Figure 2. Percentage of patients with YMDD mutations over 8 years of lamivudine treatment

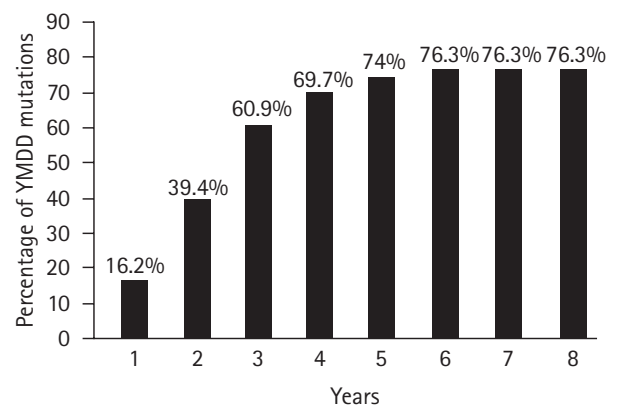
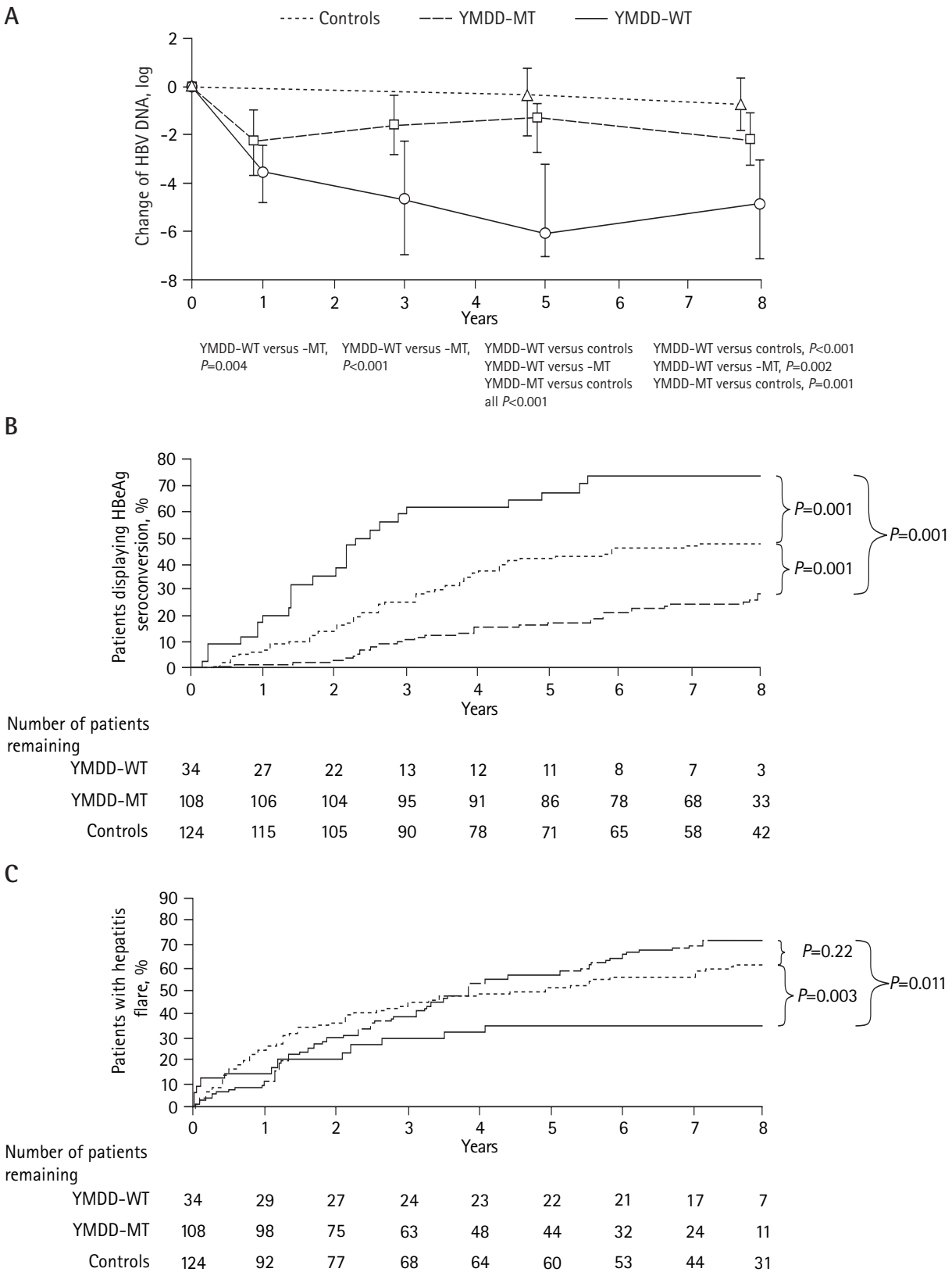


Figure 3. HBV DNA levels, HBeAg seroconversion and hepatitis flares of the study population



(A) Change of median hepatitis B virus (HBV) DNA levels (the upper and lower horizontal lines represent the values of 25th and 75th percentiles respectively). Cumulative rates of hepatitis B e antigen (HBeAg) seroconversion (B) and hepatitis flare (C) of lamivudine-treated and control patients over 8 years of follow-up. YMDD-MT, YMDD mutants; YMDD-WT, YMDD wild-type.

**Table 2.** Changes of albumin and bilirubin levels in lamivudine-treated patients and controls over years

Year	Albumin, g/l			Bilirubin, $\mu\text{mol/l}$		
	YMDD-WT	YMDD-MT	Control	YMDD-WT	YMDD-MT	Control
3	-2 (-13-+5)	-3 (-10-+14)	-2 (-12-+7)	-1 (-16-+14)	+1 (-11-+12)	0 (-14-+11)
5	-2.5 (-9-+3)* <sup>†</sup>	-4 (-12-+5) <sup>†</sup>	-4 (-13-+8)*	0 (-13-+11)	+1 (-15-+17)	+1 (-12-+15)
8	-3 (-8-+7) <sup>†</sup>	-4 (-11-+2)	-5 (-11-+7) <sup>†</sup>	-3 (-10-+8) <sup>§</sup>	+2 (-7-+19) <sup>‡</sup>	+2 (-18-+20) <sup>§</sup>

Values expressed in median (range). Minus (-) and plus (+) refer to decrease and increase of values from baseline. YMDD-MT, YMDD mutants; YMDD-WT, YMDD wild-type. \* $P=0.036$ , <sup>†</sup> $P=0.005$ , <sup>‡</sup> $P=0.045$ , <sup>§</sup> $P=0.062$  and <sup>¶</sup> $P=0.008$ .

lamivudine-treated patients. Control patients were recruited irrespective of the baseline viral load, because in Asian patients who acquire the HBV infection at birth or early childhood CHB continues to progress with very low viral load [3,18]. One study of patients from Hong Kong finds that 'it is not possible to define a single cut-off HBV DNA value for differentiating inactive carriers from patients with HBeAg-negative chronic hepatitis' [19]. Two recent studies of more than 3,500 CHB patients from Taiwan show that the risks for the development of HCC and of cirrhosis-related complications increase with increasing HBV DNA levels [20,21]. Therefore, any bias in the outcome of the present study should be in favour of the control patients because of their lower HBV DNA levels. That the cumulative risk of development of complications was higher in the control group is further proof of the beneficial effects of long-term lamivudine treatment.

The most important finding of the present study is that long-term lamivudine treatment was effective in retarding the development of cirrhosis and HCC in HBeAg-positive patients without advanced disease. This was associated with a slower decline in the albumin levels and a greater reduction of bilirubin levels. This signifies that long-term lamivudine is able to retard disease progression. With more long-term continuation of lamivudine, these differences can be expected to have clinical significance. The benefits observed in precirrhotic and cirrhotic patients with advanced disease in the study by Liaw *et al.* [5] are now confirmed in the present study in asymptomatic patients at a younger age (the median age of the lamivudine-treated patients was 33.9 years) without advanced disease with a longer treatment. These improved outcomes were observed even in the 76.3% of our patients with YMDD-MT for up to 8 years. The present study emphasizes the efficacy of continued viral suppression in patients with high viral loads.

For patients with YMDD-WT, 58.8% and 47.1% of patients had HBV DNA levels <1,000 copies/ml (171.8 IU/ml) and <35 copies/ml (6.0 IU/ml), respectively, after 8 years of lamivudine therapy. The long-term beneficial effect of lamivudine treatment in Asian patients is very

likely to be related to the persistent suppression of viral replication down to a very low level with continued therapy. Reversion of histological improvement obtained during the treatment period with adefovir has been observed upon cessation of treatment [22]. Together with the findings from our study, there is a case for prolonged continuous nucleoside/nucleotide analogue therapy in order to delay/prevent the development of cirrhosis and HCC.

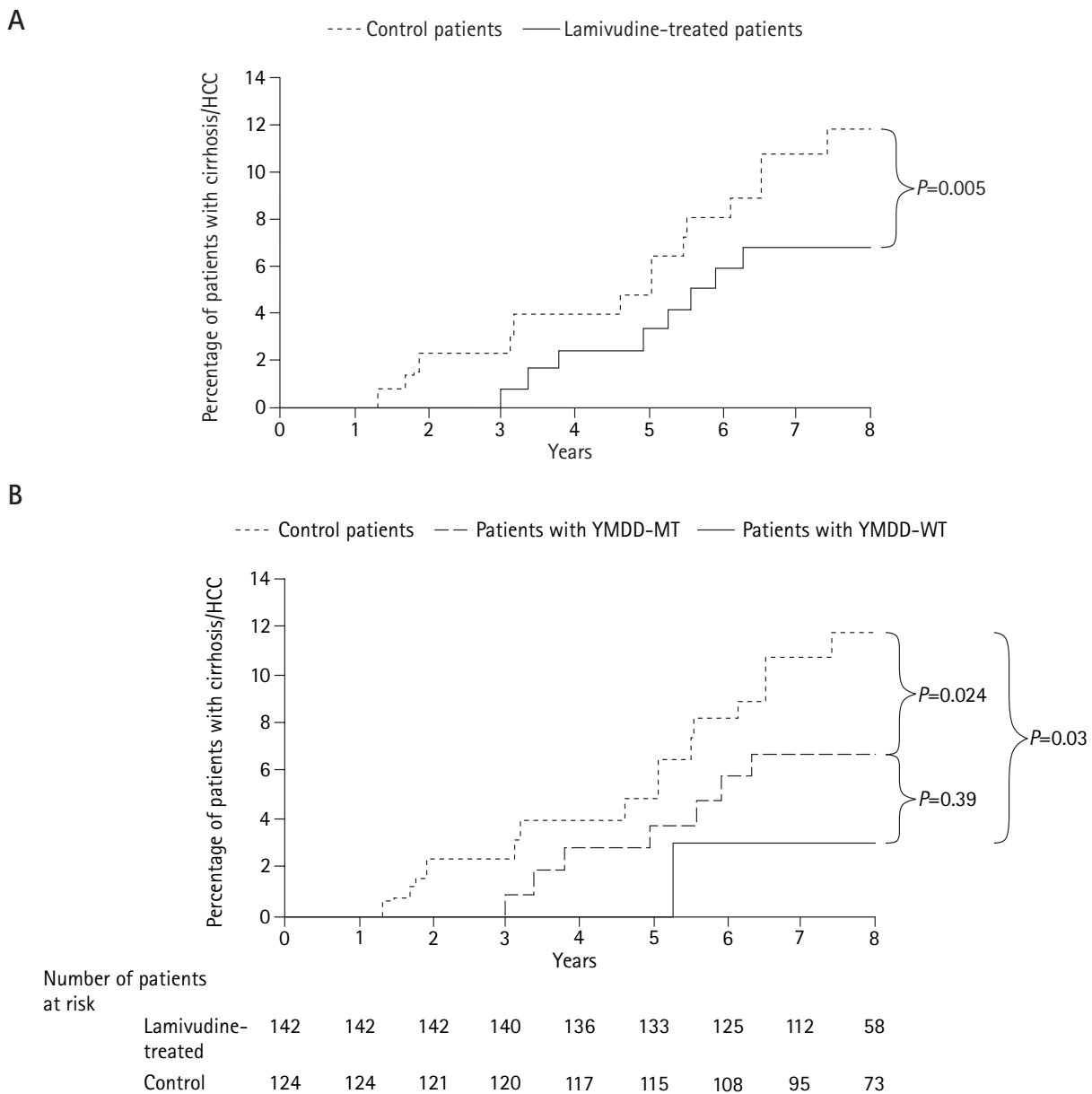
The occurrence of YMDD-MT limited the long-term use of lamivudine. In the present study, the occurrence of YMDD-MT plateaued off after 5–6 years of treatment. Twenty-four percent of patients remained without YMDD-MT after 8 years of treatment. These patients had the most favourable outcome with the highest rate of HBeAg seroconversion, lowest rate of hepatitis flare, greatest reduction of HBV DNA, slowest decline of albumin level, highest chance of normalization of ALT and, importantly, the lowest chance of development of cirrhosis and HCC. On the other hand, patients with YMDD-MT did not differ from controls in the biochemical and virological parameters, but the HBeAg seroconversion rate was higher in controls. This may be related to the significantly lower HBV DNA levels in the control patients at baseline. However, of greater clinical importance, even in patients with YMDD-MT, there was a significantly lower risk of developing cirrhosis and HCC (Figure 4) and a greater reduction of HBV DNA levels compared with controls (Figure 3). Patients with YMDD-MT who developed cirrhosis and HCC all developed the YMDD-MT within the first 3 years of therapy. This may suggest that even with YMDD-MT, patients took a longer time to develop complications than patients with no treatment. Therefore, even though patients with YMDD-MT fared worse than patients without YMDD-MT, they still had a better outcome than the untreated patients, with no additional risks of hepatitis flares and hepatic decompensation. With the availability of newer drugs like adefovir dipivoxil and entecavir effective against YMDD-MT [23,24], the problem of lamivudine resistance will be further alleviated.

The proportion of patients on lamivudine treatment with loss of HBsAg and development of anti-HBs was small. However, these patients lost HBsAg at a younger age than the control patients. In our previous study of 92 Asian patients with spontaneous HBsAg seroclearance, it has been shown that patients with HBsAg seroclearance at an older age, especially if they already have cirrhosis, are at risk of developing HCC. Therefore, HBsAg seroclearance at an earlier age with lamivudine treatment

may protect patients from developing HCC. This needs large-scale, long-term studies for confirmation.

In conclusion, long-term lamivudine treatment in clinical asymptomatic Asian hepatitis B patients at a young age was effective in retarding the development of cirrhosis and HCC through suppression of viral activity. Although the development of YMDD-MT reduced the maximal benefits from lamivudine therapy, the outcome of these patients was still better than untreated patients.

Figure 4. Cumulative rates of development of cirrhosis and/or hepatocellular carcinoma



Cumulative rates of development of cirrhosis and/or hepatocellular carcinoma of lamivudine-treated versus control patients (A) and lamivudine-treated patients with YMDD wild-type (YMDD-WT) versus patients with YMDD mutants (YMDD-MT) versus control patients (B).

## Acknowledgements

The study was performed at our own initiative and was not sponsored by any pharmaceutical company after the first 3 years of the initial lamivudine treatment. The decision to continue with lamivudine treatment for the patients was our own. The cost for the measurement of various laboratory parameters was self-funded by the Hepatology Research Fund, Department of Medicine, The University of Hong Kong.

## References

- Lai CL, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. *Lancet* 2003; **362**:2089–2094.
- World Health Organization. Fact Sheet No 204, Hepatitis B. (Updated October 2000, accessed 18 October 2005). Available from <http://www.who.int/mediacentre/factsheets/fs204/en/index.html>
- Yuen MF, Yuan HJ, Wong DKH, *et al.* Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005; **54**:1610–1614.
- Yu MW, Yeh SH, Chen PJ, *et al.* Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005; **97**:265–272.
- Liaw YF, Sung JJ, Chow WC, *et al.* Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**:1521–1531.
- Lai CL, Chien RN, Leung NW, *et al.* A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998; **339**:61–68.
- Lai CL, Yuen MF, Hui CK, Garrido-Lestache S, Cheng CT, Lai YP. Comparison of the efficacy of lamivudine and famciclovir in Asian patients with chronic hepatitis B: results of 24 weeks of therapy. *J Med Virol* 2002; **67**:334–338.
- Yuen MF, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology* 2001; **34**(4 Pt 1):785–791.
- Yuen MF, Sablon E, Yuan HJ, *et al.* Significance of hepatitis B genotype in acute exacerbation, HBeAg seroconversion, cirrhosis-related complications, and hepatocellular carcinoma. *Hepatology* 2003; **37**:562–567.
- Hammerstingl RM, Schwarz WV, Schmitt E, *et al.* Diagnostic imaging in liver cirrhosis. *Radiologe* 2001; **41**:852–867.
- Strohm WD. Ultraschalltomographie der Leber ihrer Erkrankungen. [Ultrasound tomography of the liver and its diseases.] *Z Gastroenterol* 1984; **22**:221–235. German.
- Niederau C, Heintges T, Lange S, *et al.* Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996; **334**:1422–1427.
- Korenman J, Baker B, Waggoner J, Everhart JE, Di Bisceglie AM, Hoofnagle JH. Long-term remission of chronic hepatitis B after alpha-interferon therapy. *Ann Intern Med* 1991; **114**:629–634.
- Lau DT, Everhart J, Kleiner DE, *et al.* Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 1997; **113**:1660–1667.
- Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999; **29**:971–975.
- Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* 2001; **34**:139–145.
- Yuen MF, Wong DK, Sablon E, *et al.* HBsAg seroclearance in chronic hepatitis B in the Chinese: virological, histological, and clinical aspects. *Hepatology* 2004; **39**:1694–1701.
- Yuan HJ, Yuen MF, Ka-Ho Wong D, Sablon E, Lai CL. The relationship between HBV-DNA levels and cirrhosis-related complications in Chinese with chronic hepatitis B. *J Viral Hepat* 2005; **12**:373–379.
- Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology* 2002; **36**:1408–1415.
- Chen CJ, Yang HI, Su J, *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**:65–73.
- Hoeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**:678–686.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, *et al.* Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005; **352**:2673–2681.
- Perrillo R, Hann HW, Mutimer D, *et al.* Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004; **126**:81–90.
- Chang TT, Gish RG, Hadziyannis SJ, *et al.* A dose-ranging study of the efficacy and tolerability of entecavir in lamivudine-refractory chronic hepatitis B patients. *Gastroenterology* 2005; **129**:1198–1209.

---

Accepted for publication 28 August 2007

