Lamivudine for the treatment of chronic hepatitis B

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Abstract

Lamivudine (Zeffix™) is the first of a new class of antiviral agents to become available for the treatment of chronic hepatitis B. The results of controlled clinical trials indicate that in most patients, lamivudine improves necro-inflammatory liver disease, reduces the progression of hepatic fibrosis, normalises serum alanine aminotransferase, and enhances hepatitis B e antigen (HBeAg) seroconversion. For patients with HBeAg-positive chronic hepatitis B, one year of lamivudine therapy results in HBeAg seroconversion rates similar to those obtained with a standard course of interferon-alpha. Moreover, results from two and three years of lamivudine therapy show that the cumulative HBeAg seroconversion rate continues to increase with extended lamivudine therapy. Even in the absence of HBeAg seroconversion, lamivudine therapy leads to improvements in liver disease in many patients. HBV strains (YMDD variants) with reduced *in vitro* sensitivity to lamivudine were detected in some patients after at least 9 months therapy. Although the clinical benefits to lamivudine were greatest for those patients who remained free of YMDD variants, one year of lamivudine therapy led to improvements in most response parameters compared with placebo, regardless of whether YMDD variants were detected. Controlled and open-label studies show that lamivudine may provide similar benefits to other important groups of patients with chronic hepatitis B, including those with pre-core mutant disease and those with hepatic decompensation. Lamivudine was well tolerated in all patient groups studied. The incidence of adverse events was consistently similar in patients who received lamivudine compared with those given placebo. In conclusion, extensive clinical data provide evidence that lamivudine is a well-tolerated, effective, and convenient medicine for patients with chronic hepatitis B. (Acta gastroenterol. belg., **2000**, 63, **348-358**).

Key words : lamivudine, chronic hepatitis B, clinical efficacy, safety, liver.

Introduction

At least 900,000 to 1 million people in Europe become infected with the hepatitis B virus (HBV) each year (1). As a result of these new HBV infections, about 90,000 chronic HBV carriers will develop in Europe. This is against a backdrop of an estimated 350 million chronic carriers worldwide (2), of which more than three quarters may be of Asian ethnicity (3). In Europe, chronic hepatitis B is more prevalent in Mediterranean and eastern countries than in northern or western countries.

Lamivudine (Zeffix™) is the first oral antiviral therapy approved for the treatment of chronic hepatitis B. Lamivudine is a nucleoside analogue that rapidly and profoundly suppresses hepatitis B virus (HBV) replication through inhibition of viral DNA synthesis.

The purpose of this review is to discuss the main findings of the clinical programme for lamivudine, including efficacy after at least one year and three years' of therapy, the effects of YMDD variants on clinical response parameters, and the main safety findings of the phase III studies. The efficacy of lamivudine in treating patients with severe decompensated chronic hepatitis B, and in treating or preventing post-liver transplant recurrence of HBV, is also summarised.

Clinical efficacy of Lamivudine

Clinical Pharmacology of lamivudine

Pharmacokinetic studies with lamivudine showed that the drug is rapidly absorbed after oral dosing, reaching maximum concentrations within 0.5 to 1.5 hours. About 70% of an oral dose is eliminated renally as unchanged drug (4,5). A further 5–10% of the dose is excreted as the trans-sulphoxide metabolite. Evaluation of the pharmacokinetics of lamivudine in different patient groups established that dose adjustments are only required for paediatric patients and for patients with moderate to severe renal impairment (6-8). Lamivudine is not significantly bound to plasma proteins (4) and does not interact with any drug that has been tested (9).

Dose-ranging studies

Early clinical trials showed that lamivudine has potent antiviral activity against chronic HBV infections in man (10-15). Lamivudine at a dose of 100 mg once daily provided maximal antiviral responses. Lamivudine was well tolerated and only minor adverse events were reported. Therefore, the 100-mg dose was selected for further evaluation in large controlled clinical trials. The early studies had dosing periods of 4–24 weeks and did not generally provide sustained improvements in virological or disease markers upon cessation of therapy. Consequently, the phase III studies were of longer duration (at least one year).

Design of the phase III studies

An overview of the design of the phase III studies is given in Table I. All phase III studies were randomised, controlled, and double-blind with the exception of the

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Table I. — **Overview of the phase III clinical studies of Lamivudine**

Author and Reference	Protocol	Location	Treatments	Number of patients
Lai *et al.* (18)	B3009	Asia	Lamivudine 100 mg ; 25 mg ; (1 yr) Placebo	358
Liaw *et al.* (27,28)	B3018	Asia	Lamivudine 100 mg ; 25 mg ; (2 yr) Placebo	334
Leung *et al.* (29,30)	B3018	Asia	Lamivudine 100 mg ; 25 mg ; (3 yr) Placebo	334
Dienstag *et al.* (16)	A3010	US	Lamivudine 100 mg ; Placebo	143
Schalm *et al.* (19)	B3010	Europe, Canada	Lamivudine 100 mg ; IFN ; Lamivudine 100 mg and IFN	229
Schiff *et al.* (17)	AB3011[1]	Europe, US	Lamivudine 100 mg ; Placebo ; Lamivudine 100 mg and IFN	238
Tassopoulos *et al.* (25)	B3014[2]	Europe	Lamivudine 100 mg ; Placebo	125

IFN = Interferon-α.
[1] IFN failures.
[2] HBeAg–ve, anti-HBe+ve (presumed precore mutant) chronic hepatitis B.

two studies involving comparisons with interferon-alpha (IFN-α). These two studies could not be fully blinded because of ethical constraints that prohibit using placebo injections.

Entry criteria for the phase III trials were designed to select adult patients with evidence of non-decompensated necro-inflammatory liver disease due to chronic infection with HBV. Specific criteria included a diagnosis of chronic hepatitis B with evidence of active viral replication (hepatitis B surface antigen (HBsAg)-positive for at least six months ; HBV DNA-positive and hepatitis B e antigen (HBeAg)-positive at screening and for at least one month before screening) as well as moderately elevated serum alanine aminotransferase (ALT) concentrations (generally 1.3 to 10 times the upper limit of the normal reference range (ULN)) and/or histological evidence of necro-inflammatory liver disease. Patients with anti-HBe positive (presumed pre-core mutant) chronic hepatitis B, and patients who had previously failed to respond to IFN-α therapy were also studied in separate trials.

Placebo-controlled studies in HBeAg positive chronic hepatitis B

Three placebo-controlled studies (16-18) evaluated the efficacy of one year of lamivudine therapy in a total of 808 patients with HBeAg-positive chronic hepatitis B. In Schalm *et al.*, (19) the lamivudine treatment arm provided additional data on the response to lamivudine monotherapy.

Virological response

Serum HBV DNA concentrations were measured to determine the effects of lamivudine therapy on HBV replication. Among patients receiving lamivudine, the median serum HBV DNA level fell rapidly, remaining at least 94% below the pre-treatment value throughout each study (16-19). Suppression of serum HBV DNA was similar in Chinese (16) and Western (16) patients, and in treatment-naïve patients (16,18,19). In all studies, serum HBV DNA fell to undetectable levels at least once during therapy in more than 89% of patients receiving lamivudine.

HBeAg seroconversion (loss of detectable HBeAg and appearance of anti-HBe) occurred in a significantly higher proportion of treatment naïve patients receiving lamivudine compared with placebo ($p < 0.04$) (Fig. 1) (16, 18). Results were also similar when one year of lamivudine therapy is compared with a standard course of IFN-α (19). The proportion of patients receiving lamivudine for one year who attained HBeAg seroconversion was similar among these studies. These seroconversions were stable after discontinuation of lamivudine in at least 91% of patients for a median six months of follow-up (20).

The cumulative HBeAg seroconversion rate was higher in patients with elevated serum ALT pre-treatment. For example, in the Asian study, HBeAg seroconversion occurred in 5% of the 87 patients receiving lamivudine with pre-treatment ALT less than two times the upper limit of the normal range (ULN), in 34% of the 53 patients with ALT greater than two times the ULN, and in 64% of the 11 patients with pre-treatment ALT greater than five times the ULN (21). Corresponding

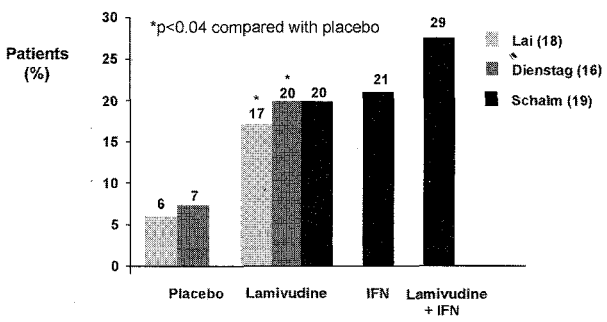

Fig. 1. — HBeAg seroconversion in three trials of treatment naïve patients.

rates for the placebo group were 2%, 7%, and 14% respectively.

Improvement in liver disease

Liver histology was evaluated using two methods. The first was a comparison of Knodell histologic activity index (HAI) scores before and after therapy. "Improvement" was defined as a two-point or greater decrease in HAI score ; "worsening" was defined as a two-point or greater increase. The second method involved blinded ranking of paired pre- and post-treatment biopsy specimens for each patient, evaluated for severity of necro-inflammatory activity and fibrosis.

In the placebo-controlled studies, liver histology improved in a significantly higher proportion of patients receiving lamivudine, compared with those receiving placebo (67% versus 30% (16) ; and 62% versus 30% (18) respectively ; $p < 0.001$). Correspondingly, liver disease worsened in fewer patients receiving lamivudine, compared with placebo. Improvements in liver histology were similar in Chinese and Western patients, and in treatment-naïve patients compared with patients who had previously received IFN-α therapy (16-19). A further clinical study in Japanese patients produced similar results : liver histology improved in 19/20 (95%) patients by at least two points after one year of lamivudine therapy (22).

The results obtained from comparing changes in Knodell score corresponded closely to the results of blinded rankings of paired pre- and post-treatment liver biopsy specimens. In this latter analysis, necrosis and inflammation improved in a higher proportion of patients who received lamivudine, compared with patients who received placebo (16-19).

In the Asian trial, 44% of patients with normal ALT before treatment had improved liver histology after one year of therapy with lamivudine (18). The rate of histological response to lamivudine was somewhat higher (56%) in patients with elevated ALT pre-treatment, possibly due to the greater scope for improvement in patients with more severe disease. This finding indicates that some patients with normal ALT nevertheless have active necro-inflammatory liver disease that can be improved with lamivudine.

Lamivudine therapy can improve liver histology regardless of whether HBeAg loss or seroconversion occurs. In Lai *et al.*, liver histology improved in 46% of patients who remained HBeAg positive at the end of one year of lamivudine therapy (18). Liver histology improved in an even greater proportion of patients who lost detectable HBeAg (64%). Thus in the context of lamivudine therapy, loss of HBeAg usually leads to concomitant histological improvement, but liver histology may improve even without HBeAg loss or seroconversion.

Fibrosis of the liver can lead to cirrhosis and liver failure, and a primary therapeutic objective for patients with chronic hepatitis B is to reverse fibrosis or to halt its progression. The effects of lamivudine upon hepatic fibrosis were assessed by blinded comparison of pre- and post-treatment biopsy specimens. In the two placebo-controlled lamivudine monotherapy studies in treatment-naïve patients, significantly fewer lamivudine-treated patients experienced worsening of liver fibrosis compared with placebo-treated patients (3% and 6% of patients worsened on lamivudine versus 15% and 27% on placebo in the US (16) and Asian (18) studies respectively, $p < 0.01$).

Many patients (34-47%) receiving lamivudine had improvements in hepatic fibrosis during their one year of therapy (16,19). A similar rate of improvement (35%) was observed in a study of Japanese patients (22). Although improvement in fibrosis was not analysed statistically in these studies, the data suggest that viral suppression induced by lamivudine may reverse pre-existing fibrosis in some patients, as well as reducing progression.

Retrospective analysis of integrated phase III data showed that significantly fewer patients receiving lamivudine developed cirrhosis, compared with those receiving placebo, (1.8% versus 7.1% ; $p = 0.04$) (23). Development of cirrhosis in this analysis was defined as progression from a pre-treatment Knodell fibrosis score of zero, one, or three to a post-treatment score of four.

Among those patients with elevated serum ALT concentrations at entry, sustained serum ALT normalisation occurred in significantly more patients receiving lamivudine compared with placebo ($p < 0.001$ in each placebo-controlled study) (16-19). The integrated results of phase III trials (17-19) showed that lamivudine therapy generally led to improvements in serum ALT during the first few months of therapy, with the median ALT concentration approaching the normal range within six months. Similar findings were reported for a large, 429-patient study of lamivudine carried out in China (24). After one year of lamivudine, sustained ALT normalisation occurred in 60% of the patients in the lamivudine group, compared with 28% in the placebo group ($p < 0.01$) (24).

Studies in HBeAg negative chronic hepatitis B

A placebo-controlled study showed that with the exception of HBeAg responses, the response to lamivudine is similar in patients with HBeAg–ve, anti-HBe+ve (presumed pre-core mutant) hepatitis B, compared with the patients with HBeAg-positive (wild-type) HBV infections who were enrolled in other phase III studies (25). Serum HBV DNA levels declined sharply at the onset of therapy, and remained low or undetectable throughout the six-month, double-blind part of the study. Significantly more patients receiving lamivudine (63%), compared with placebo (6%), had normal serum ALT and undetectable serum HBV DNA after six months of therapy (defined as a complete response ; $p < 0.001$). Among patients who received lamivudine for 12

months, liver histology improved in 55%, similar to clinical studies of other patient groups. Sustained normalisation of serum ALT on therapy occurred in significantly more patients treated with lamivudine for 12 months compared with those who received placebo (67% versus 5%, respectively ; $p < 0.001$).

HBeAg loss and seroconversion are not endpoints of therapy of HBeAg negative hepatitis B, since detectable anti-HBe in serum is characteristic of this condition. For the same reason, HBeAg is not a useful marker for predicting the durability of therapeutic responses post-treatment. Nevertheless, when lamivudine was discontinued after one year, therapeutic benefits persisted in some patients at the end of the 4-month post-treatment follow-up period (26) ; serum HBV DNA remained negative in 43% of patients and ALT remained normal in 24%, while both responses persisted simultaneously in 16% of patients. Long-term treatment may therefore be a consideration in patients with HBeAg negative chronic hepatitis B.

Combination therapy : Lamivudine with IFN-α

Two phase III studies evaluated the efficacy of lamivudine used in combination with IFN-α for the treatment of chronic hepatitis B (17,19). The rationale for these studies was based on the differing modes of action of IFN-α and lamivudine, and the possibility that they may interact synergistically (Table I). Neither study showed a clear advantage for the combination over lamivudine alone.

Lamivudine therapy for one year led to HBeAg loss and HBeAg seroconversion rates that were similar to those obtained with a standard course of IFN-α (19). In treatment-naïve patients, the seroconversion rate for lamivudine/IFN-α combination therapy (29%) was higher than that for either lamivudine (20%) or IFN-α monotherapy (21%) (19). These differences were not statistically significant in the primary intent-to-treat analysis. However a retrospective per-protocol analysis found a significant difference ($p = 0.02$) between IFN-α/lamivudine combination therapy (36%) and lamivudine monotherapy (19%). In the study of IFN non-responders (17), combination therapy had no advantage over lamivudine monotherapy in terms of HBeAg seroconversion.

Long-term efficacy of Lamivudine

The response of Asian patients with chronic hepatitis B to two and three years of lamivudine therapy has also been evaluated (Table I) (27–30). HBV DNA suppression was maintained in most patients who received a total of two years of lamivudine (27). Ninety-four percent of the patients in this study tested negative for serum HBV DNA at least once, and at the end of two years, 52% of these patients showed sustained clearance of serum HBV DNA.

The cumulative rate of HBeAg seroconversion increases progressively with extended lamivudine therapy. Among the 58 patients treated for three years with lamivudine, the cumulative HBeAg seroconversion rate increased from 22% after one year of therapy to 40% after three years of therapy (29,30). Within this group, 38% of the patients with pre-treatment ALT at least two times the ULN attained HBeAg seroconversion during the first year of lamivudine therapy. This increased to 65% after three years of therapy (Fig. 2) (30).

Liver histology continued to improve during lamivudine therapy that was extended beyond one year. In a subset of 19 patients with evaluable liver biopsy specimens after two years of therapy, 17 (89%) showed improvements of at least 2 points in the Knodell necro-inflammatory score (28). Extended therapy with lamivudine also led to a sustained normalisation in ALT levels for those patients that had elevated serum ALT concentrations at entry. After two years of lamivudine therapy, 32/64 patients (50%) achieved sustained ALT normalisation (27).

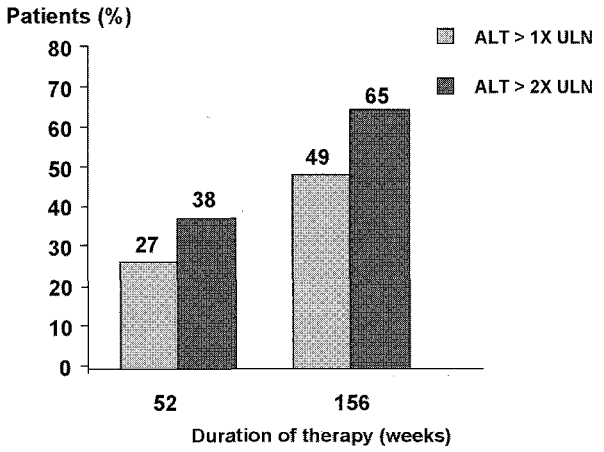

Fig. 2. – HBeAg seroconversion in patients with elevated serum ALT (n = 58).

YMDD variants

After extended lamivudine therapy, genetically altered strains of HBV were identified in some patients (31,32). These HBV variants have mutations in the gene encoding the HBV polymerase (in and near the YMDD motif) and are not sensitive to inhibition by lamivudine *in vitro*. (33,34). YMDD variants do not replicate as effectively as wild-type HBV *in vitro* most likely due to the lower affinity of the viral polymerase for its nucleotide substrates (33–37). Studies were undertaken to characterise these YMDD variants, to determine their incidence in patients receiving lamivudine therapy, and to assess the effects of these variants upon clinical response parameters.

Occurrence of YMDD variants

YMDD variants were detected in very few chronic hepatitis B patients during the first 6 months of lamivudine therapy (32). After one year of therapy, YMDD variants were detected in 14-32% of patients in the different phase III studies. After two and three years of therapy with lamivudine, YMDD variants were detected in 42% and 52% of Asian patients respectively (27,29). Pre-treatment serum HBV DNA concentration, HAI score, ALT, and body mass index correlated positively with the subsequent emergence of YMDD variants during one year of lamivudine therapy.

When lamivudine therapy ended after one year, the proportion of patients with detectable YMDD variants declined during the three- to four-month post-treatment follow-up period. During follow-up after three studies, the prevalence of YMDD variants declined from 32% to 29%, from 31% to 21%, and from 27% to 21% (16,17,19) Similar reversion was observed after discontinuation of lamivudine in other studies of patients with HBeAg-positive chronic hepatitis B (38,39), in patients with HBeAg negative chronic hepatitis B (25) and in liver transplant patients (40).

In addition, most patients with YMDD variants at the end of therapy had nearly pure populations of a single variant strain, without detectable wild-type HBV (16,19). However, by the end of the 12- to 16-week drug-free follow-up period, most patients had mixed populations of HBV strains. This suggests that removal of drug selection pressure leads to re-emergence of wild-type HBV as the dominant strain.

Clinical changes in patients with YMDD variants

Virological response in patients with YMDD variants

Integrated data from one year of lamivudine therapy showed that the median serum HBV DNA concentration pre-treatment was higher in patients who subsequently developed YMDD variants (138 pg/mL) compared with those who did not (75 pg/mL) (41). Regardless of whether YMDD variants eventually emerged, however, lamivudine induced rapid and profound HBV DNA suppression, with most patients becoming HBV DNA negative during treatment.

After two or three years of lamivudine therapy, the median serum HBV DNA concentration remained substantially below the pre-treatment value in those who developed YMDD variants. Even among patients with YMDD variants after one year of therapy, the median HBV DNA concentration two years' later remained below the pre-treatment value and below the median for patients receiving placebo. However, serum HBV DNA was higher for patients with YMDD variants compared with patients without detectable variants (29).

In studies of treatment-naïve patients (16,18), the HBeAg seroconversion rate was significantly higher in patients receiving lamivudine compared with those receiving placebo, regardless of whether YMDD variants were detected (41). Among patients receiving lamivudine, the emergence of YMDD variants reduced but did not prevent HBeAg seroconversion (16,18,42). After three years of lamivudine, HBeAg seroconversion occurred in 6/27 (22%) patients with YMDD variants, compared to 12/24 (50%) patients who remained free of variants (29). Preliminary PCR data suggest that HBeAg seroconversion is associated with the lowest levels of serum HBV DNA regardless of which HBV genotype predominates (43).

Improvement in liver disease in patients with YMDD variants

Analyses of integrated phase III data were performed with and without adjustment for pre-treatment variables that might affect histological or HBeAg responses. In both types of analyses, patients with YMDD variants had a significantly higher probability of histological improvement (≥ 2-point reduction in Knodell HAI) at one year compared with the placebo group ($p < 0.003$) (41). However for patients receiving lamivudine, the adjusted comparison showed that histological improvements occurred in significantly more patients who remained free of YMDD variants, compared with those in whom YMDD variants appeared ($p < 0.002$). These results suggest that lamivudine therapy improves liver histology despite the emergence of YMDD variants, but such improvements occur more frequently in the absence of YMDD variants. Histological assessment of patients treated for two years suggests continued improvement in liver disease despite the presence of YMDD variants (28).

Lamivudine generally resulted in improvements in serum ALT regardless of whether YMDD variants were detected during therapy. After one year of lamivudine, median serum ALT decreased from 1.7 times the ULN to 0.7 times the ULN in patients without YMDD variants, and from 2.5 × ULN to 1.2 × ULN in patients with YMDD variants. Transient ALT elevations were observed in some patients during emergence of YMDD variants. Among 55 Asian patients who received lamivudine for at least two years, > 2-fold ALT elevations occurred in 13 patients following emergence of YMDD variants. These ALT increases were associated with rising serum levels of HBV DNA. However, 8/13 (62%) of these patients subsequently attained HBeAg seroconversion (44). This pattern is similar to that of natural spontaneous HBeAg seroconversion in patients with wild-type HBV, and suggests that ALT elevations associated with the emergence of YMDD variants may sometimes precede a beneficial clinical outcome.

Safety of Lamivudine

Integrated data from the phase III clinical trials showed that the incidence of adverse events during therapy was similar for patients receiving lamivudine and placebo, and most were mild and not considered to

Table II. — **Frequency of post-treatment ALT elevations in phase III clinical studies of Lamivudine* (% of patients with event)**

Response Criteria	Placebo (n = 66)	Lamivudine (n = 215)	IFN-α (n = 68)	Lamivudine + IFN-α (n = 134)
ALT ≥ 2 × baseline concentration	20	26	25	32
ALT ≥ 3 × baseline concentration	8	19	16	16
ALT ≥ 2 × baseline concentration and > 500 IU/L	9	14	9	9
ALT ≥ 2 × baseline concentration and Bilirubin ≥ 2 × ULN and ≥ 2 × baseline	2	1	1	0

* Data are derived from studies with post-therapy observation periods. These include Schalm *et al.* (19), Dienstag *et al.* (16), and Schiff *et al.* (17) for lamivudine data ; Dienstag *et al.* (16) and Schiff *et al.* (17) for placebo ; Schalm *et al.* (19) and Schiff *et al.* (17) for lamivudine/IFN-α combination ; and Schalm *et al.* (19) for IFN-α.

Table III — Liver transplant studies with Lamivudine

Reference and protocol number	Location	Number of Patients	Patient Population
Perrillo *et al.* (47) A3005	USA	64	HBV recurrence after liver transplantation
Perrillo *et al.* (48,49) A2006	USA	77	ESLF due to CHB, awaiting liver transplantation
Grellier *et al.* (50) B2008	Europe	26	ESLF due to CHB, awaiting liver transplantation
Bain *et al.* (51) B2021	Canada	5	ESLF due to CHB, awaiting liver transplantation

ESLF = end-stage liver failure.
CHB = chronic hepatitis B.

be related to lamivudine (16-19,25,27,45). Analyses of the subset of adverse events considered to be possibly or probably related to study drug or of unknown relationship revealed similar frequencies of such events for patients treated with lamivudine or placebo. The incidence of adverse events was markedly higher in treatment groups that included IFN-α (17,19,45). Adverse events were similar in patients receiving IFN-α compared with IFN-α/lamivudine combination therapy. The proportions of patients experiencing laboratory abnormalities corresponding to toxicity grades 3 and 4 (adapted from World Health Organisation criteria (46)) were also similar for the lamivudine and placebo groups.

HBV replication and serum ALT often return to pre-treatment levels if lamivudine is stopped before HBeAg seroconversion (10,15). Infrequently, patients who discontinue lamivudine may experience post-treatment elevations in serum ALT that exceed pre-therapy concentrations. The incidence of post-treatment ALT elevations ≥ 2 × baseline values was similar among patients who received lamivudine, IFN-α or IFN-α/lamivudine combination, and only slightly higher than in patients who received placebo (Table II). This suggests that many of the mild post-treatment ALT elevations observed in these studies may be related to natural disease fluctuations rather than the treatment received.

Compared with placebo-treated patients, lamivudine-treated patients experienced a somewhat higher incidence of ALT elevations ≥ 3 × baseline values (corresponding to a grade 3 toxicity), and of ALT elevations ≥ 2 × baseline values, coupled with absolute ALT values > 500 IU/L (45). However, similarly low proportions of patients who received lamivudine or placebo experienced post-treatment ALT elevations associated with serious clinical adverse events, bilirubin elevations, or other signs of hepatic insufficiency. In practice, ALT monitoring may facilitate detection of such events if lamivudine is discontinued before HBeAg seroconversion. Such monitoring may be particularly valuable for patients with advanced hepatitis B in whom there is reduced hepatic reserve.

Lamivudine in decompensated hepatitis B and liver transplantation

Impairment of liver function due to chronic hepatitis B is a potentially life-threatening condition and creates an urgent need for therapeutic intervention. Similarly, *de novo* and recurrent hepatitis B in liver transplant recipients are associated with a high rate of graft loss and are often life threatening. Open-label studies examined the efficacy of lamivudine for the treatment of patients with severe decompensated chronic hepatitis B, and for the treatment or prevention of post-liver transplant recurrence of HBV (47–51).

Clinical studies

The effects of lamivudine in patients with end-stage liver failure (ESLF) awaiting transplantation were studied in three open-label studies (Table III) (48–51). These studies focused on prophylactic treatment of

HBsAg-positive liver transplant candidates both before and after transplantation in order to prevent post-transplant recurrence. The pre-surgical phases of these studies provided data about the effects of lamivudine on the most severe form of decompensated, life-threatening chronic hepatitis B. A further study investigated the treatment of patients who already showed evidence of post-transplant hepatitis B, and required treatment to prevent or control renewed liver disease and graft failure (47). The objective of these studies was to suppress HBV replication and to prevent (prophylaxis studies) or suppress post-transplant recurrence, in order to stabilise or improve liver disease.

Patients were enrolled into the three prophylaxis studies if they had ESLF due to chronic hepatitis B (seropositive for HBsAg) and were listed for liver transplantation. Patients were enrolled into the post-transplant recurrence study if they showed evidence of HBV infection (HBV DNA and HBsAg positive) after liver transplantation, with histological evidence of disease in the grafted liver.

Response to Lamivudine in patients with ESLF

The largest prophylaxis study enrolled 77 patients, 27 of whom did not undergo anticipated liver transplantation and received lamivudine for a median 762 days (49). In these 27 patients, markers of both HBV infection and liver disease improved after the start of lamivudine therapy. Similar to patients with less severe disease, serum HBV DNA declined rapidly, becoming undetectable in 63% of the 19 patients who were HBV DNA positive before treatment.. At the last study visit, serum ALT was normal in 57% of the 23 patients who had elevated ALT before treatment. Serum bilirubin and albumin also improved after the start of lamivudine therapy, indicating the beneficial effects of lamivudine on liver function. Serum bilirubin concentrations normalised in 18% of patients and mean serum albumin increased from 3.1 mg/dl at baseline to 3.4 mg/dl at last study visit. Survival data indicate that six patients died from liver failure during the study, three during the first three months. The surviving 21 patients have received lamivudine for a median duration of 917 days. Most remain on therapy and are doing well clinically. Notably, one of the surviving patients improved to the point where he was removed from the transplant list.

Patients responded to lamivudine to a similar extent before transplantation in the studies reported by Grellier *et al.* (50) and Bain *et al.* (51). Serum HBV DNA became undetectable within four weeks in all twelve patients who were positive before treatment in Grellier *et al.*, and in the five patients enrolled in Bain *et al.*. Most patients showed concomitant improvements in serum ALT before transplantation.

An open-label, uncontrolled evaluation of long-term lamivudine treatment of 35 patients with decompensated cirrhosis due to chronic HBV infection included patients with Child-Pugh scores (8 : 25 were categorised as Child-Pugh class C, the most severely ill group, and 10 patients were categorised as class B (52). Five patients died (all class C) during the first six months of lamivudine therapy due to liver failure (four patients) or hepatocellular carcinoma (one patient). Seven further patients (five class C, two class B) received liver transplants soon after the start of the study.

The remaining 23 patients were treated for > 6 months. In this group, significant improvements occurred in markers of necro-inflammatory disease (ALT, AST) and liver function (albumin and bilirubin), and 22 patients showed sustained, progressive clinical and biochemical improvement, as defined by a (2-point decrease in the Child-Pugh score. One patient did not improve and received a liver transplant after 16 months of therapy, but subsequently died. Two patients died after extended (17 and 31 months) lamivudine therapy from bacterial peritonitis and hepatocellular carcinoma, respectively. Overall 20 of the 23 patients treated for > 6 months remained alive after completing a median 19 months of treatment. Among the 15 non-transplanted class C patients who survived > 6 months, nine improved to class B and five to class A.

Six patients attained hepatitis B e-antigen (HBeAg) seroconversion during the study, and one also lost detectable HBsAg. The cumulative incidence of recurrent serum HBV DNA due to YMDD variants (confirmed by genotypic analysis) was 10% and 25% after one and two years respectively, similar to that observed in studies of patients with non-decompensated CHB. No effect of viral breakthrough on clinical parameters was reported (52).

Lamivudine prophylaxis to prevent post-transplant HBV recurrence

Among liver transplant recipients who received lamivudine both before and after surgery, patient clinical status and survival appear to be improved, compared with prior experience of transplant recipients with post-surgical HBV recurrence. Thus lamivudine appears to reduce the rate of HBV reinfection when given pre- and post-liver transplantation.

In the largest prophylaxis study, 47 patients were transplanted, receiving a median 80 days of lamivudine therapy pre-transplant and 367 days post-transplant (48). Of the 34 patients for whom week 52 data (post-transplant) were available, 71% remained HBsAg negative, 79% were HBV DNA negative.

Similar findings were reported for 17 patients who received liver transplants in Grellier *et al.* (50), and four patients who received transplants in Bain *et al.* (51). In the latter study, all four transplanted patients became HBV DNA negative by PCR post-transplant. Two of these patients remained free of detectable HBV DNA, with normal liver function, after 12 and 104 weeks respectively post-transplant.

Long-term survival data indicate that four patients died after transplant surgery of causes unrelated to HBV (53). Two patients died 19 and 23 months post-transplant respectively due to graft rejection. The remaining 11 patients survive, ten of whom continue to receive lamivudine 18-48 months after surgery. Eight of these 10 patients remain free of detectable HBV DNA by PCR assay, with normal serum ALT.

Treatment of post-transplant HBV recurrence with Lamivudine

Lamivudine also suppresses HBV recurrences that occur after liver transplantation. The large study of post-transplant recurrence investigated the responses to lamivudine in 52 patients with HBV recurrence who had been transplanted a median of four years before entry into the study (47). Half had received hepatitis B immune globulin (HBIg) therapy (unsuccessfully) to prevent post-transplant HBV recurrence. During the 12 months of this study, most patients showed marked improvements in virological markers. Serum HBV DNA concentrations declined significantly at both 26 and 52 weeks compared with pre-treatment values ($p = 0.001$), and became undetectable in most patients. Biochemical indicators of liver necro-inflammatory disease (ALT) and function (bilirubin and albumin) also improved significantly during the one year of therapy. This suggests that suppression of HBV replication in liver transplant recipients, as in patients with less severe hepatitis B, leads to improvement of liver disease. These findings are supported by comparison of liver biopsies taken before and after six months of lamivudine. Improvement (≥ 2 points) in the Knodell necro-inflammatory score was reported for 56% of patients, whereas 13% showed worsening. There was no change in hepatic fibrosis, which is not unexpected in view of the relatively short duration of therapy before biopsy.

Lamivudine used in combination with HBIg also appears to prevent or delay recurrence of HBV after liver transplantation. In a study of 14 patients treated both before and after liver transplantation, HBV was undetectable by PCR assay in the 13 surviving patients (one patient died of unrelated causes) at a median of 346 days after transplantation (54). At a median 394 days post-transplant, median serum aspartate aminotransferase, ALT, bilirubin, and alkaline phosphatase values were within the normal range for the 13 survivors.

Summary and conclusions

Extensive clinical data provide evidence that lamivudine is a well-tolerated, effective, and convenient medicine for patients with all forms of chronic hepatitis B. One year of lamivudine therapy led to suppression of serum HBV DNA, increased rates of HBeAg seroconversion, reduced hepatic necro-inflammation, reduced progression of hepatic fibrosis and progression to cirrhosis, and normalisation of serum ALT. Extended therapy with lamivudine for 3 years led to an increase in the rate of HBeAg seroconversion and continued viral suppression. The clinical benefits of lamivudine are greatest for those patients who remain free of YMDD variants. However, patients with YMDD variants can still achieve HBeAg seroconversion, and can maintain lower serum HBV DNA and ALT levels than at baseline. Lamivudine is well tolerated ; the frequency of adverse events is similar for patients receiving lamivudine and placebo. Lamivudine may provide similar benefits to other patients with hepatic decompensation and those undergoing a liver transplant. Therefore, lamivudine represents an important therapeutic advance for the treatment of patients with chronic hepatitis B.

Acknowledgements

Funding for the studies reviewed was provided by Glaxo Wellcome Research and Development. We thank David Harrison for writing and editing assistance during preparation of the manuscript.

References

1. VAN DAMME P., TORMANS G., BEUTELS P. *et al.* Hepatitis B prevention in Europe : a preliminary economic evaluation. *Vaccine*, 1995, **13** (suppl. I) : 54-57
2. DAVEY S. *State of the World's Vaccines and Immunization*. Geneva : World Health Organization, 1996, 76-82.
3. MAYNARD J.E. Hepatitis B : global importance and need for control. *Vaccine*, 1980, **8** (suppl.) :18-20.
4. JOHNSON M.A., MOORE K.H.P., YUEN G.J. *et al.* A review of the clinical pharmacokinetics of lamivudine. *Clin. Pharmacokinetics*, 1999, **36** : 41-66.
5. JOHNSON M.A., HORAK J., BREUEL P. The pharmacokinetics of lamivudine in patients with impaired hepatic function. *Eur. J. Clin. Pharmacol.*, 1998, **54** : 363-366.
6. HEALD A.E., HSYU P.H., YUEN G.J. *et al.* Pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with renal dysfunction. *Antimicrob. Agents Chemother.*, 1996, **40** : 1514-1519.
7. JOHNSON M.A., VERPOOTEN G.A., DANIEL M.J. Single dose pharmacokinetics of lamivudine in subjects with impaired renal function and the effect of haemodialysis. *Brit. J. Clin. Pharmacol.*, 1998, **46** : 21-27.
8. SOKAL E., ROBERTS E.A., MIELI-VERGANI G. *et al.* Dose-finding and safety of lamivudine (LAM) in children and adolescents with chronic hepatitis B. *Hepatology*, 1998, **28** : 489A.
9. MOORE K.H., YUEN G.J., RAASCH R.H. *et al.* Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. *Clin. Pharmacol. Ther.*, 1996, **59** : 550-558.
10. NEVENS F., MAIN J., HONKOOP P. *et al.* Lamivudine therapy for chronic hepatitis B : a six-month randomized dose-ranging study. *Gastroenterology*, 1997, **113** : 1258-1263.
11. TYRRELL D.L.J., MITCHELL M.C., DE MAN R.A. *et al.* Phase II trial of lamivudine for chronic hepatitis B. *Hepatology*, 1993, **18** : 112A.
12. LAI C.L., CHING C.K., TUNG A.K.M. *et al.* Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers : a placebo-controlled trial. *Hepatology*, 1997, **25** : 241-244.
13. TANIKAWA K. Anti-HBV activity of lamivudine in Japanese. *Abstracts of the IASL Biennial Scientific Meeting*, Capetown 18-24 February 1996, abstract 66T.
14. LIAW Y.F., CHIEN R.N., SHEEN I.S. *et al.* A randomized, controlled, dose-ranging study of lamivudine in patients with chronic hepatitis B. *Abstracts of the International AGA/Singapore Gastroenterological Meeting*, 7-9 Sep 1995.
15. DIENSTAG J.L., PERRILLO R.P., SCHIFF E.R. *et al.* A preliminary trial of lamivudine for chronic hepatitis B infection. *N. Engl. J. Med.*, 1995, **333** : 1657-1661.

16. DIENSTAG J.L., SCHIFF E.R., WRIGHT T.L. *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N. Engl. J. Med.*, 1999, **341** : 1256-1263.
17. SCHIFF E., KARAYALCIN S., GRIMM I. *et al.* A placebo controlled study of lamivudine and interferon alpha-2b in patients with chronic hepatitis B who previously failed interferon therapy. *Hepatology*, 1998, **28** : 388A.
18. LAI C.L., CHIEN R.N., LEUNG N.W. *et al.* A one-year trial of lamivudine for chronic hepatitis B. *N. Engl. J. Med.*, 1998, **339** : 61-68.
19. SCHALM S.W., HEATHCOTE J., CIANCIARA J. *et al.* Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection : a randomized trial. *Gut*, 2000, **46** : 562-568.
20. SCHIFF E., CIANCIARA J., KOWDLEY K. *et al.* Durability of HBeAg seroconversion after lamivudine monotherapy in controlled phase II and III trials. *Hepatology*, 1998, **28** : 489A.
21. CHIEN R.N., LIAW Y.F., ATKINS M. *et al.* Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. *Hepatology*, 1999, **30** : 770-774.
22. SUZUKI Y., KUMADA H., IKEDA K. *et al.* Histological changes in liver biopsies after one year of lamivudine treatment in patients with chronic hepatitis B infection. *J. Hepatol.*, 1999, **30** : 743-748.
23. GOODMAN Z., DHILLON A.P., WU P.C. *et al.* Lamivudine treatment reduces progression to cirrhosis in patients with chronic hepatitis B. *J. Hepatol.*, 1999, **30** (Suppl. 1) : 59.
24. YAO G.B., WANG B.E., CUI Z. *et al.* A randomized double-blind placebo-controlled study of lamivudine in the treatment of patients with chronic hepatitis B virus infection. *Chinese Med. J.*, 1999, **112** : 387-391.
25. TASSOPOULOS N.C., VOLPES R., PASTORE G. *et al.* Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. *Hepatology*, 1999, **29** : 889-896.
26. TASSOPOULOS N.C., VOLPES R., PASTORE G. *et al.* Post lamivudine treatment follow up of patients with HBeAg negative chronic hepatitis B. *J. Hepatol.*, 1999, **30** (Suppl. 1) : 117.
27. LIAW Y.F., LEUNG N.W.Y., CHANG T.T. *et al.* Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. *Gastroenterology*, 2000, **119** : 172-180.
28. LEUNG N., WU P.C., TSANG S. *et al.* Continued histological improvement in Chinese patients with chronic hepatitis B with 2 years lamivudine. *Hepatology*, 1998, **28** : 489A
29. LEUNG N.W.Y., LAI C.L., CHANG T.T. *et al.* Three year lamivudine therapy in chronic HBV. *J. Hepatology*, 1999, **30** (Suppl. 1) : 59.
30. CHANG T.T., LAI C.L., LIAW Y.F. *et al.* Enhanced HBeAg seroconversion rates in Chinese patients on lamivudine. *Hepatology*, 1999, **28** : 420A.
31. BARTHOLOMEW M.M., JANSEN R.W., JEFFERS L.J. *et al.* Hepatitis B virus resistance to lamivudine given for recurrent infection after orthotopic liver transplantation. *Lancet*, 1997, **349** : 20-22.
32. LAI C.L., LIAW Y.F., LEUNG N.W.Y. *et al.* Genotypic resistance to lamivudine in a prospective, placebo-controlled multicentre study in Asia of lamivudine therapy for chronic hepatitis B infection : incidence, kinetics of emergence, and correlation with disease parameters. *Hepatology*, 1997, **26** : 259A.
33. ALLEN M.I., DESLAURIERS M., ANDREWS C.W. *et al.* Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. *Hepatology*, 1998, **27** : 1670-1677.
34. LING R., HARRISON T.J. Functional analysis of mutations conferring lamivudine resistance on hepatitis B virus. *J. General Virol.*, 1999, **80** : 601-606.
35. MELEGARI M., SCAGLIONI P.P., WANDS J.R. Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective. *Hepatology*, 1998, **27** : 628-633.
36. ONO-NITA S.K., KATO N., SHIRATORI Y. *et al.* YMDD motif in hepatitis B virus DNA polymerase influences on replication and lamivudine resistance : a study by *in vitro* full-length viral DNA transfection. *Hepatology*, 1999, **29** : 939-945.
37. BOCK T.C., TORRESI J., TILLMANN H.L. *et al.* Replication fitness of hepatitis B virus polymerase mutants after antiviral treatment following liver transplantation. *Hepatology*, 1999, **28** : 299A.
38. CANE P.A., MUTIMER D., RATCLIFFE D. *et al.* Analysis of hepatitis B virus quasispecies changes during emergence and reversion of lamivudine resistance in liver transplantation. *Antiviral Therapy*, 1999, **4** : 7-14.
39. CHAYAMA K., SUZUKI Y., KOBAYASHI M. *et al.* Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. *Hepatology*, 1998, **27** : 1711-1716.
40. GAILLARD R.K., BARNARD J., LOPEZ V. *et al.* Kinetic analysis of HBV polymerase YMDD variants. *Abstr. 39th ICAAC*, Washington DC : ASM Press, 1999, pg. 447.
41. ATKINS M., HUNT C.M., BROWN N. *et al.* Clinical significance of YMDD mutant hepatitis B virus (HBV) in a large cohort of lamivudine-treated hepatitis B patients. *Hepatology*, 1998, **28** : 319A.
42. GARRETT L., DIENSTAG J.L., GAUTHIER J. *et al.* Hepatitis B e-antigen (HBeAg) seroconversion in two patients with evidence of genotypic resistance following extended lamivudine treatment. *Hepatology*, 1997, **26** : 431A.
43. GAUTHIER J., BOURNE E.J., LUTZ M.W. *et al.* Quantitation of hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. *J. Infect. Dis.*, 1999, **180** : 1757-62
44. LIAW Y.F., CHIEN R.N., YEH C.T. *et al.* Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology*, 1999, **30** : 567-72.
45. LEUNG N.W.Y., DIENSTAG J., SCHIFF E.R. *et al.* Clinical safety profile of lamivudine treatment in a large cohort of hepatitis B patients. *Hepatology*, 1998, **28** : 587A.
46. MILLER A.B., HOOGSTRATEN B., STAQUET M. *et al.* Reporting results of cancer treatment. *Cancer*, 1981, **47** : 207-214.
47. PERRILLO R.P., RAKELA J., DIENSTAG J.L. *et al.* Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology*, 1999, **29** : 1581-1586.
48. PERRILLO R.P., SCHIFF E.R., DIENSTAG J.L. *et al.* Lamivudine for prevention of recurrent hepatitis B after liver transplantation : final results of a U.S./Canadian multicenter trial. *Hepatology*, 1999, **28** : 222A.
49. PERRILLO R.P., SCHIFF E.R., DIENSTAG J.L. *et al.* Lamivudine for suppression of viral replication in patients with decompensated chronic hepatitis B. *Hepatology*, 1999, **28** : 301A.
50. GRELLIER L., MUTIMER D., AHMED M. *et al.* Lamivudine prophylaxis against re-infection in liver transplantation for hepatitis B cirrhosis. *Lancet*, 1996, **348** : 1212-1215.
51. BAIN V.G., KNETEMAN N.M., MA M.M. *et al.* Efficacy of lamivudine in chronic hepatitis B patients with active viral replication and decompensated cirrhosis undergoing liver transplantation. *Transplantation*, 1996, **62** : 1456-1462.
52. VILLENEUVE J.P., CONDREAY L.D., WILLEMS B., POMIER-LAYRARGUES G., FENYVES D., BILODEAU M., LEDUC R., PELTEKIAN K., WONG F., MARGULIES M., HEATHCOTE E.J. Lamivudine for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology*, 2000, **31** : 207-210.
53. MUTIMER D.J., GRELLIER L., BARRETT C.A. *et al.* Lamivudine without HBIg for prevention of graft infection by hepatitis B ; long term follow-up. *Hepatology*, 1999, **28** : 301A.
54. MARKOWITZ J.S., MARTIN P., CONRAD A.J. *et al.* Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology*, 1998, **28** : 585-589.