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# Liver Disease—Significant Improvement With Lamivudine

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The natural history of chronic hepatitis B virus (HBV) infection is highly variable, ranging from a benign course to one of shortened life expectancy. Liver histology represents an accurate tool for assessing progressive liver disease, and has been used in five recent Phase III clinical trials of the oral nucleoside analogue, lamivudine, 100 mg/day, in patients with chronic hepatitis B. Significant improvements in the Knodell histological activity index (HAI) score were reported with lamivudine, with greater decreases noted after 2 years of therapy, consistent with continued alanine transaminase (ALT) normalisation. Histological data showed that lamivudine therapy can resolve or lessen the progression of fibrosis, and reduce the progression to cirrhosis in patients with chronic hepatitis B. These trials also showed that lamivudine provoked significant enhancement of hepatitis B e antigen (HBeAg) seroconversion compared with placebo, and had a profound effect on serum HBV DNA, resulting in rapid suppression of viraemia. The emergence of variants with a mutation in the YMDD (tyrosine-methionine-aspartate-aspartate) motif did not cause significant worsening of the Knodell HAI score. In conclusion, lamivudine is the first oral antiviral therapy for the treatment of chronic hepatitis B. It reduces significantly the severity of liver disease and reduces progression to cirrhosis. In addition, because lamivudine is well tolerated it represents a viable therapeutic option that may improve the prognosis of patients with chronic hepatitis B. ***J. Med. Virol. 61:380–385, 2000.***


**KEY WORDS:** chronic hepatitis B; liver histology; nucleoside analogue; YMDD variant; treatment

## INTRODUCTION

Chronic hepatitis B is a potentially fatal infection associated with significant, progressive liver disease. Over 75% of the world's 350 million chronic carriers of hepatitis B virus (HBV) reside in Asia and the western Pacific regions [Davey, 1996; Gust, 1996], and up to one-third of individuals chronically infected with HBV are expected to develop serious, progressive liver disease, leading to cirrhosis and liver cancer [Zuckerman, 1996, 1999]. Seventy-five to ninety-five percent of cases of hepatocellular carcinoma world-wide can be attributed to infection with this virus [Boag, 1991].

The natural history of HBV carriers is highly variable, ranging from a benign course to one of shortened life expectancy. Regular monitoring of viral serology and liver biochemistry may aid the identification of individuals with chronic disease activity who are at risk of disease progression. Histological features, however, can give a more direct and relevant assessment, and are particularly important in evaluating the efficacy of therapeutic agents.

There are various therapeutic goals in the treatment of chronic hepatitis B, depending on the severity of infection and the stage of disease. As cirrhosis and hepatocellular carcinoma result in significant morbidity and mortality, the prevention of these complications is an important objective. Until recently, the treatment of hepatitis B has relied on the use of interferon (IFN) alpha. Poor tolerability, the need for parenteral administration, and concerns about safety in patients with hepatic decompensation, however, limit the value of this agent [Pessoa and Wright, 1999]. In addition, IFN alpha has a low response rate, particularly in Asian-Pacific populations in whom the incidence of hepatitis B carriage is the highest [Lai, 1999]; furthermore, the cost of therapy in these regions may be prohibitive. Finally, IFN alpha may have a limited effect on the progression to hepatocellular carcinoma in HBV-infected individuals with cirrhosis [International Interferon-Alpha Hepatocellular Carcinoma Study Group, 1998].

Lamivudine, an oral nucleoside analogue that provides potent inhibition of HBV replication [Chang et al., 1992; Furman et al., 1992;], is now licensed in many

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countries for the treatment of chronic hepatitis B. Lamivudine acts directly against HBV resulting in a sustained hepatitis B e antigen (HBeAg) seroconversion, reduced progression of hepatic fibrosis and reduced progression to cirrhosis [Dusheiko, 1998; Goodman et al., 1999]. Thus, treatment with lamivudine may improve the prognosis of patients with chronic hepatitis B.

## HISTOPATHOLOGY OF CHRONIC HEPATITIS B

Chronic hepatitis B is characterised by varying degrees of inflammation, that may be portal, periportal (interface hepatitis or piecemeal necrosis) or lobular, and fibrosis, that can be categorised as portal, portal-to-portal or portal-to-central. Other histological features of chronic hepatitis B include ground glass hepatocytes and dysplasia. The latter feature is of particular concern, as it is likely to be indicative of molecular changes within the liver.

Several semi-quantitative and quantitative scoring systems are available for the evaluation of liver histology and disease activity. One quantitative assessment is the Knodell histological activity index (HAI) [Knodell et al., 1981], that represents the sum of scores for periportal bridging necrosis (0–10), intralobular degeneration and focal necrosis (0–4), portal inflammation (0–4) and fibrosis (0–4). The sum of the first three components is used as an index of necro-inflammatory activity, whereas the fibrosis component is important for disease staging (modified HAI or Ishak Fibrosis Score). Some of the Phase III lamivudine trials have also used a ranked assessment scoring system to evaluate the therapeutic efficacy of different agents. The histological appearance of paired liver biopsy samples (pre- and post-treatment) was assessed centrally by pathologists who remained blinded to information relating to the sequence in which the biopsies were taken and the patient's therapeutic regimen.

## LAMIVUDINE—PHASE III STUDIES

Five recent Phase III studies have investigated the efficacy and safety of lamivudine administered for at least 1 year in patients with chronic hepatitis B. Of the four placebo-controlled studies, one conducted in Europe and Canada studied patients with HBeAg-negative/HBV DNA-positive chronic hepatitis B who were presumed to be infected with the HBV pre-core mutant [Tassopoulos et al., 1999]; one conducted in the US, Europe and Israel, included HBeAg-positive patients with raised serum alanine transaminase (ALT) concentrations who had been non-responsive to previous treatment with IFN alpha [Schiff et al., 1998]; and one conducted in Asia studied HBeAg-positive/HBV DNA-positive patients [Lai et al., 1998]. A further US placebo-controlled trial studied untreated viraemic patients not treated previously who were HBeAg-positive and had raised serum ALT concentrations [Dienstag et al., 1999]. A similar patient group from Europe, Canada and Australia was studied by Schalm et al. [2000] who compared lamivudine or IFN alpha either alone or in combination (lamivudine followed by lamivudine plus IFN alpha). Treatment was extended for up to 3 years [Leung et al., 1999] for patients studied by Lai et al. [1998].

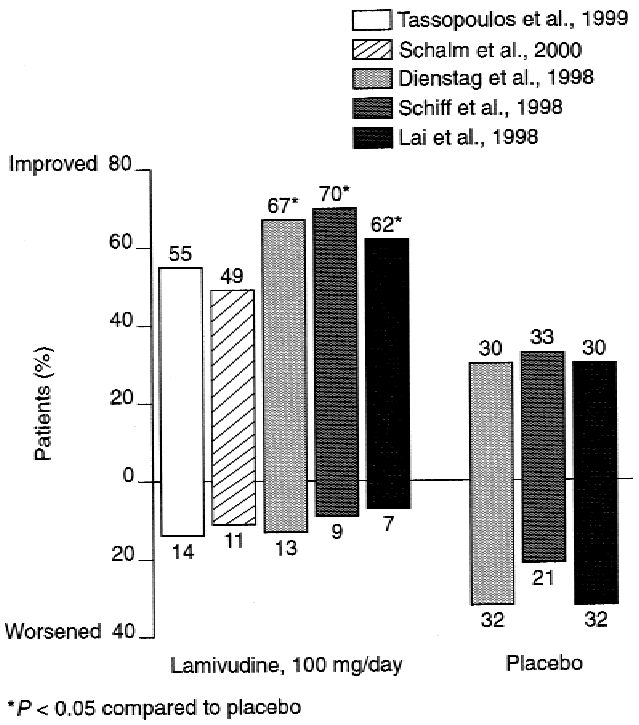


Fig. 1. Changes in total Knodell histological activity index score.

In all trials, evaluation of treatment efficacy was undertaken using a variety of histological assessments, including Knodell HAI score and ranked assessment, biochemical assessment (serum ALT), and virological assessments. The primary focus, however, was to evaluate the effect of lamivudine on histological parameters of liver disease.

### Histological Assessment

***Knodell HAI score.*** In all five Phase III trials, histological assessment was performed for all patients with evaluated data at Weeks 0 and 52. Response (i.e., improvement in liver histology) was defined as a reduction in the Knodell HAI score by at least 2 points, and progression (i.e., worsening) of liver disease was defined as an increase in the Knodell HAI score by at least 2 points. Of the four placebo-controlled studies, three [Lai et al., 1998; Schiff et al., 1998; Dienstag et al., 1999] showed a significantly higher proportion of lamivudine-treated patients achieving improvement in liver histology after 1 year compared with those receiving placebo (67% vs. 30%, 62% vs. 30%, and 70% vs. 33%, respectively; $P < 0.05$) (Fig. 1). More importantly, a lower proportion of lamivudine-treated patients had evidence of worsening liver histology compared with those receiving placebo (13% vs. 32%, 7% vs. 32%, and 9% vs. 21%, respectively). In one study [Tassopoulos et

al., 1999], histological response was only evaluated in patients who received lamivudine. Data from this study, however, were consistent with findings from the other three studies. At 1 year, 55% of evaluated patients showed histological improvement, 21% showed no change and 14% had evidence of disease progression.

Data reported by Schalm et al. [2000] were generally consistent with the four placebo-controlled studies, with histological improvement evident in 49% of evaluated patients treated with lamivudine, 46% treated with IFN alpha and 37% treated with the combination. Moreover, the proportion of lamivudine-treated patients with evidence of disease progression was low (11%) and consistent with data from all four studies.

***Ranked assessment.*** Ranked assessment of pre- and post-treatment biopsy specimens showed that the rate of improvement of hepatic necro-inflammation was significantly higher ($P < 0.01$) in patients receiving lamivudine compared with those receiving placebo (66–82% vs. 30–46%) (Fig. 2a). Placebo patients also had a higher incidence of deterioration compared with lamivudine-treated patients (21–38% vs. 3–10%, respectively). Tassopoulos et al. [1999] reported that 36% of lamivudine-treated patients showed improvement in hepatic necro-inflammatory activity, 57% showed no change and 7% of patients deteriorated.

Patients receiving lamivudine also showed a greater improvement in the fibrosis score compared with those receiving placebo (Fig. 2b). Additionally, greater reductions in the progression of fibrosis were noted in trials conducted in Caucasian patients [Dienstag et al., 1999; Schalm et al., 2000; Schiff et al., 1998] than in Asian patients [Lai et al., 1998]. This is due most likely to lower baseline fibrosis scores among the Asian patients in this study. The incidence of deterioration was also significantly lower ($P \leq 0.01$) with lamivudine compared with placebo (6% vs. 27% [Dienstag et al., 1999]; 3% vs. 15% [Lai et al.,1998], respectively).

***Fibrosis score.*** Assessment of progression in disease staging, using the Ishak Fibrosis Score, showed a greater rate of reduction with lamivudine than with placebo (Fig. 3a), and a correspondingly lower incidence of deterioration with lamivudine compared with placebo. Moreover, reduction in the fibrosis score was generally greater in lamivudine-treated patients than in the patients treated with IFN alpha either alone or in combination with lamivudine (Fig. 3b).

***Progression to cirrhosis.*** An exploratory integrated analysis [Goodman et al., 1999] of data from three of the studies [Lai et al., 1998; Dienstag et al., 1999; Schalm et al., 2000] showed that 1.8% (4/219) of patients progressed to cirrhosis after receiving lamivudine, 100 mg/day, compared with 7.1% (7/99) of patients receiving placebo and 9.5% (4/42) of patients receiving IFN alpha. The reduction with lamivudine was significantly superior to that noted with placebo ($P < 0.04$). There was no statistical testing for the comparison of lamivudine and IFN alpha because of the small number of patients.

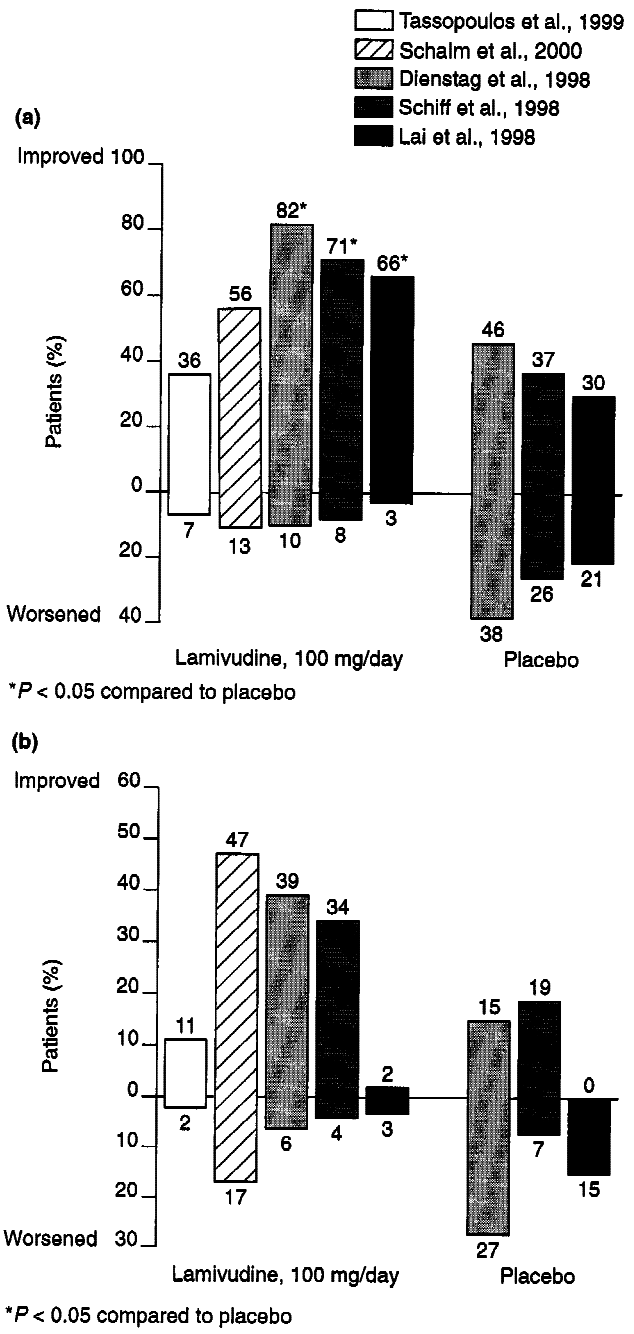


Fig. 2. Evaluation of (**a**) improved hepatic necroinflammation and (**b**) reduced progression of fibrosis by ranked assessment of pre-treatment and post-treatment biopsy specimens.

***Influence of baseline HBV DNA and ALT values.*** The influence of baseline concentrations of HBV DNA and serum ALT on improvement in liver histology was investigated [Lai et al., 1998]. The histological response to lamivudine did not seem to be affected by baseline HBV DNA values (either ≤100 pg/ml or >100 pg/ml) (Fig. 4a). Moreover, there was only a

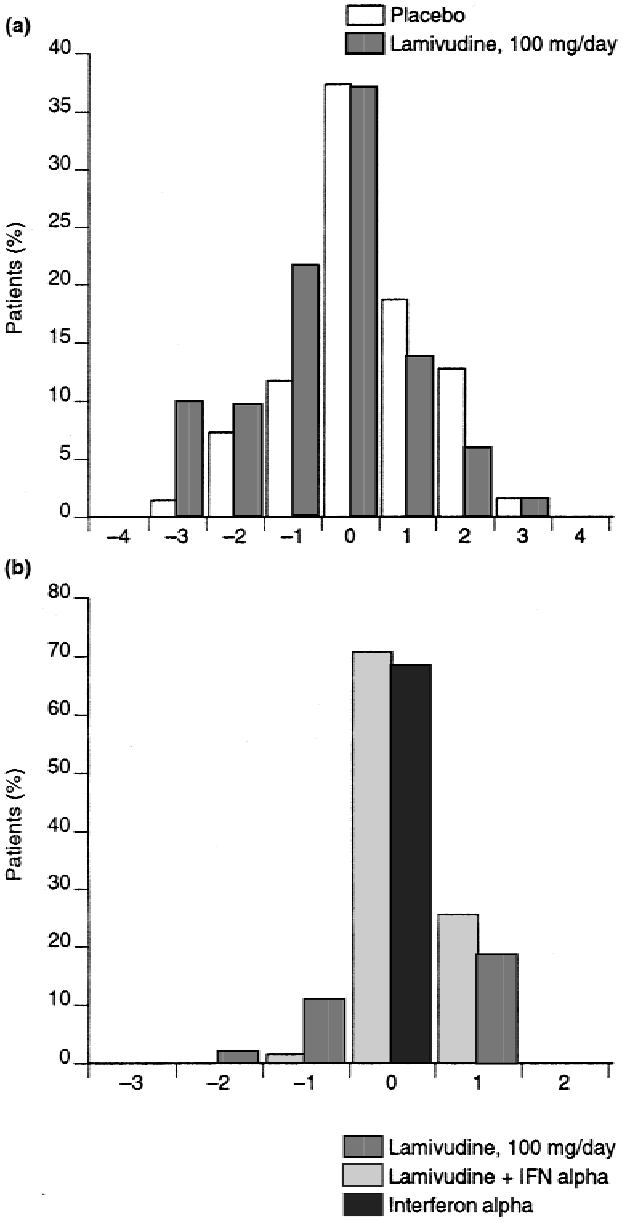


Fig. 3. Effect of lamivudine on the Ishak Fibrosis Score in studies by (**a**) Dienstag et al. and (**b**) Schalm et al. [2000].

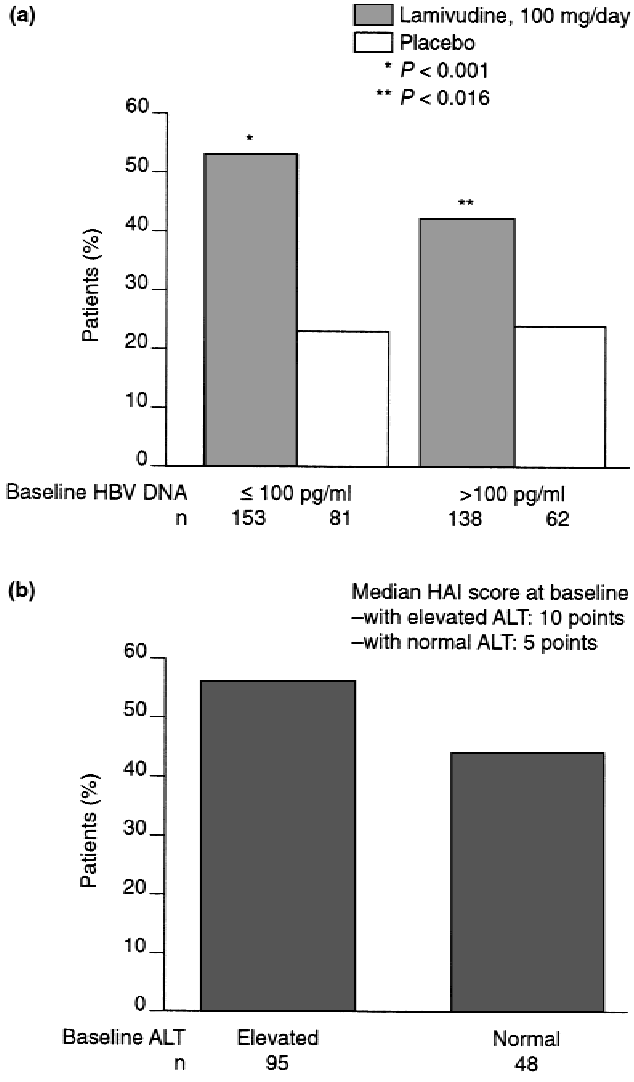


Fig. 4. Relationship between histological improvement and (**a**) baseline hepatitis B virus DNA and (**b**) serum alanine amino transferase (ALT) concentration [Lai et al., 1998]. HAI, histology activity index.

small difference in histological response rates between lamivudine-treated patients with normal or elevated pretreatment serum ALT concentrations (44% vs. 56%, respectively) (Fig. 4b).

### ALT Response

In all five Phase III studies, a sustained serum ALT response was achieved by a significantly higher proportion of lamivudine-treated patients than placebo patients (41–72% vs. 7–24%, respectively, $P < 0.001$) [Lai et al., 1998; Schiff et al., 1998; Dienstag et al., 1999], IFN alpha (40% vs. 17%, respectively, $P = 0.007$) [Schalm et al., 2000] or combination therapy (44% vs. 18%, respectively, $P = 0.005$) [Schiff et al., 1998].

### HBeAg Seroconversion

The proportion of lamivudine-treated patients who achieved HBeAg seroconversion (16–18%) was similar in all four trials studying HBeAg-positive patients [Lai et al., 1998; Schiff et al., 1998; Dienstag et al., 1999; Schalm et al., 2000]. Hence, histological improvement occurs independently of seroconversion.

## LAMIVUDINE—LONG-TERM CLINICAL EXPERIENCE

The Asian placebo-controlled study [Lai et al., 1998] has now extended into Year 5. Data are available from the first 3 years of the study [Lai et al., 1998; Liaw et al., 1998; Leung et al., 1999]. In all, 58 patients were assigned lamivudine 100 mg/day for 3 years, and median serum HBV DNA and ALT concentrations were recorded throughout the study (Fig. 5).

After initiation of lamivudine therapy, serum HBV

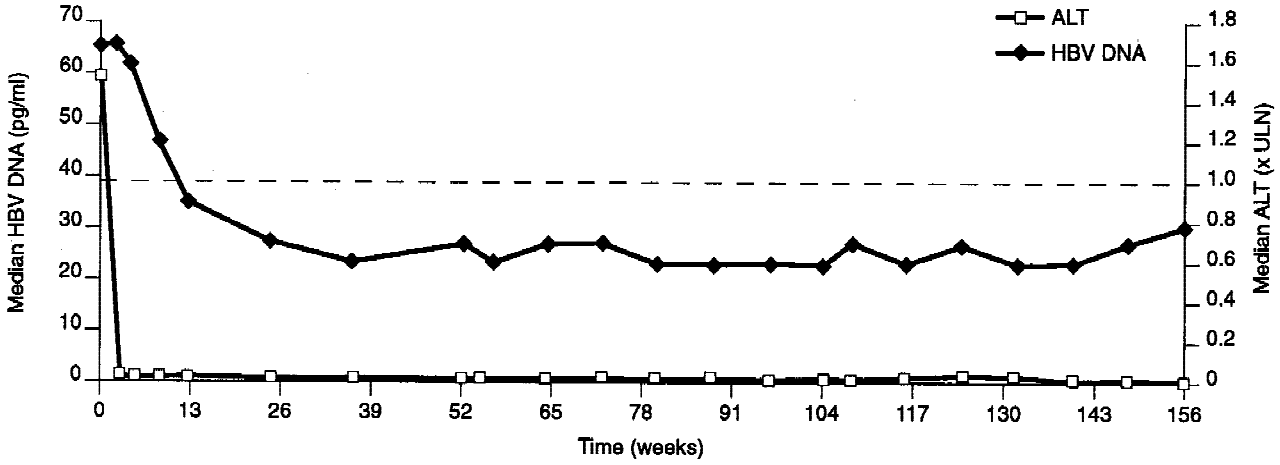


Fig. 5. Median hepatitis B virus (HBV) DNA and alanine amino transferase (ALT) values during 3 years' treatment with lamivudine [Lai et al., 1998; Leung et al., 1999]. ULN, upper limit of normal.

DNA concentrations fell rapidly, with a median reduction of 97% after 2 weeks of treatment and 98% throughout the study. Although 66% of patients had elevated pretreatment serum ALT concentrations, values fell to below the upper limit of normal (ULN) within the first 3 months. Values then remained low (around 0.6 × ULN) with 72% of patients showing a sustained ALT response at 1 year [Lai et al., 1998]. When biopsy samples were taken, patients who had received 2 years of lamivudine therapy had a reduction in the HAI score of 8 points, whereas those who had received 1 year of lamivudine therapy before or after 1 year of placebo had a reduction of around 5 points [Leung et al., 1999]. Histological improvements were noted even in patients who did not experience HBeAg seroconversion.

## IMPACT OF YMDD VARIANT HBV ON HISTOLOGICAL IMPROVEMENT

Long-term data showed that the incidence of genotypic mutations in the YMDD (tyrosine-methionine-aspartate-aspartate) HBV locus, that confers reduced sensitivity to lamivudine, increased over time, from 14% after 1 year of treatment [Lai et al., 1998], to 42% after 2 years [Liaw et al., 1998], and 49% after 3 years [Leung et al., 1999]. At the end of Year 3, 82 patients from all treatment groups underwent a liver biopsy. These patients included those treated initially with lamivudine 25 mg/day or placebo during the first year of therapy [Lai et al., 1998], those who suffered a relapse when switched to placebo, and those who developed breakthrough infections due to YMDD variants and were then given lamivudine 100 mg/day.

Despite the development of YMDD variant HBV, most patients maintained histological improvement over the 3-year period. Improvement in liver histology, relative to baseline, was reported for 68% (25/37) of patients without YMDD variant throughout the three years, 58% (11/19) of patients who had YMDD variant HBV for less than 1 year, 47% (9/19) of patients with the YMDD variant for 1–2 years, and for 71% (5/7) patients with the YMDD variant for 2–3 years. Deterioration in liver histology, relative to baseline, was reported for 22% (8/37) of patients without YMDD variant throughout the three years, 32% (6/19) of patients who had YMDD variant HBV for less than 1 year, 47% (9/19) of patients with the YMDD variant for 1–2 years, and for 14% (1/7) patients with the YMDD variant for 2–3 years (Table I) [Leung et al., 1999].

## CONCLUSIONS

Clinical signs and symptoms are of limited use in assessing disease severity in chronic hepatitis B as they are only evident in patients with late-stage liver disease. Although the replicative activity of the virus can be assessed using blood biochemistry and virological parameters, such as HBeAg and more particularly serum HBV DNA, liver histology provides a more accurate tool for evaluating progression and prognosis of liver disease. Although histological findings are conventionally described as chronic persistent hepatitis and chronic active hepatitis, histological grading is also used as it provides more information on the degree of severity of necro-inflammation, and the staging of liver disease.

The findings of these recent Phase III studies in chronic hepatitis B show that treatment with lamivudine improved significantly the Knodell HAI score, with greater decreases noted after 2 years of therapy, consistent with continued normalisation of ALT concentrations. Histological data showed that lamivudine therapy can resolve or lessen the progression of fibrosis, and reduce the progression to cirrhosis in patients with chronic hepatitis B. These trials also showed that lamivudine provoked significant enhancement of HBeAg seroconversion compared with placebo, and had a profound effect on serum HBV DNA levels, resulting in rapid and sustained suppression of viraemia.

One important clinical concern in the long-term management of chronic hepatitis B is whether the

TABLE I. Effect of YMDD Variant on Liver Histology in a Long-Term Trial of Lamivudine, 100 mg/day, in Chronic Hepatitis B

| | Duration of YMDD variant (years) | | | |
|---|---|---|---|---|
| | 0 | <1 | 1–2 | >2 |
| Number of patients | 37 | 19 | 19 | 7 |
| Improvement | 25 (68%) | 11 (58%) | 9 (47%) | 5 (71%) |
| No change | 4 | 2 | 1 | 1 |
| Deterioration | 8 (22%) | 6 (32%) | 9 (47%) | 1 (14%) |

emergence of YMDD variant HBV has any significant impact on the histological features of disease. Evaluation of data from these Phase III studies (and follow-up), however, show that the emergence of YMDD variant HBV does not seem to result in a significant amelioration of the histological benefit gained with lamivudine treatment.

In conclusion, lamivudine represents a viable therapeutic option for chronic hepatitis B. Treatment with lamivudine significantly reduces the severity of liver disease and reduces the progression of hepatic fibrosis. Lamivudine has an excellent safety profile and may improve the prognosis of patients with chronic hepatitis B.

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