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Lamivudine for Hepatitis B in Clinical Practice

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Lamivudine is a potent, once-daily, oral antiviral therapy that is effective and well tolerated in most patient groups with chronic hepatitis B virus infection, including those with pre-core mutant infection. Studies to date show that lamivudine suppresses serum viral replication, causing reductions in serum hepatitis B virus (HBV) DNA and enhancing hepatitis B e antigen (HBeAg) seroconversion (loss of HBeAg plus presence of antibodies to HBeAg [anti-HBe]). Lamivudine also improves liver disease, as shown by normalisation of alanine transaminase (ALT) levels and reduced progression to cirrhosis. Lamivudine is effective in patients who are interferon (IFN) alpha naïve and in those who have failed to respond to IFN alpha, and it suppresses HBV in decompensated liver disease and in liver transplantation. Variants with mutations in the YMDD (tyrosine–methionine–aspartate–aspartate) motif may emerge with prolonged lamivudine therapy, but most patients maintain clinical control. Lamivudine has a safety profile similar to that of placebo and it is better tolerated than IFN alpha. In conclusion, lamivudine represents a major advance in the therapeutic options available for the management of patients with chronic hepatitis B and should now be considered the drug of choice for most patients who require treatment. ***J. Med. Virol. 61: 386–391, 2000.*** © 2000 Wiley-Liss, Inc.

KEY WORDS: chronic hepatitis B; safety; nucleoside analogue; YMDD variant; treatment

INTRODUCTION

Hepatitis B is a potentially fatal liver disease and one of the most common infectious diseases in the world. Chronic hepatitis B is the world's ninth leading cause of death [Boag, 1991; Vail, 1997], causing up to 2 million deaths annually [Zuckerman, 1997]. Until very recently, the only treatment available for the management of hepatitis B was interferon (IFN) alpha. Now that lamivudine is available, many more patients with chronic hepatitis B will have access to an effective new treatment. Most patients will be eligible for lamivudine therapy, in contrast to the limited number of patients eligible for IFN alpha therapy [Hoofnagle, 1990; Gitlin, 1997; Hoofnagle and Di Bisceglie, 1997]. Safety and efficacy data from controlled clinical trials have established the utility of lamivudine for the treatment of chronic hepatitis B. The experience to date can be used to provide guidelines to assist the management of these patients. This review discusses the use of lamivudine for the routine management of patients with hepatitis B. The main issues considered are those of efficacy, safety and when to terminate therapy.

EFFICACY DATA FOR LAMIVUDINE

Results from controlled clinical trials indicate that lamivudine is an important new therapeutic option for the treatment of patients with chronic hepatitis B. A positive response to lamivudine treatment is indicated by the suppression of viral replication and an improvement in liver disease. Markers for the inhibition of hepatitis B virus (HBV) replication include HBV DNA and hepatitis B e antigen (HBeAg) loss, and HBeAg seroconversion (HBeAg loss plus the presence of antibodies to HBeAg [anti-HBe]). Markers for improvements in liver disease include serum alanine amino transferase (ALT) normalisation (indicating improved necro-inflammatory liver disease) and histological improvement or reduced progression of hepatic fibrosis [Dienstag et al., 1998; Schlam et al., 2000; Lai et al., 1998; Schiff et al., 1998a]. Preventing the progression to cirrhosis may reduce the risk of hepatocellular carcinoma.

LAMIVUDINE SUPPRESSES HBV REPLICATION

Lamivudine suppresses HBV replication in virtually all patients, including those with pre-core mutant HBV infection. Integrated data from the Phase III trials indicate that there is a profound fall in serum HBV DNA within 2 weeks of initiating treatment (Fig. 1). Response to treatment may be a result of either a direct effect of lamivudine on HBV alone or a combined effect

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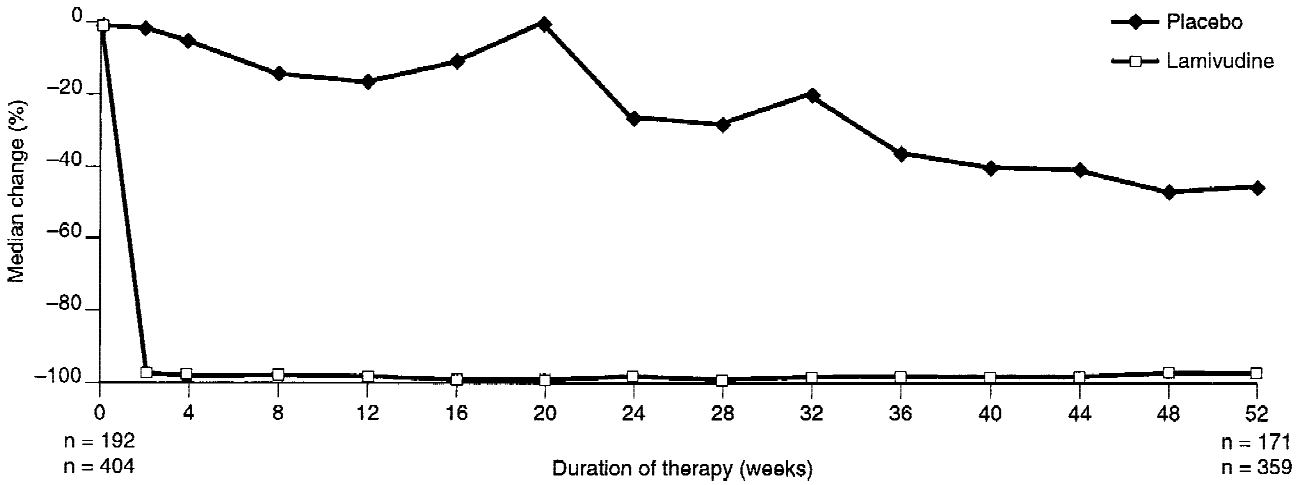

Fig. 1. Suppression of hepatitis B virus DNA during treatment with lamivudine—composite data from Phase III clinical trials. Adapted from Zeffix™ Lamivudine Product Monograph. GlaxoWellcome, 1999.

with enhanced cell-mediated immune responses that may follow the reduction in viral load and replication [Boni et al., 1998]. Unlike IFN alpha [Perrillo, 1994; Marinos et al., 1994; Gaeta et al., 1995; Hassanein et al., 1996; Hoofnagle and Di Bisceglie, 1997], lamivudine does not seem to cause flares of liver disease, that is, perhaps, surprising in the light of the increased T-cell response. The reason for this is not clear. The therapeutic goal for lamivudine is to suppress HBV replication, to such an extent that HBV DNA becomes undetectable in serum; in this way, the infection is progressively cleared. Figure 1 shows that lamivudine does produce profound inhibition of HBV replication.

Phase III trials showed that 1 year of lamivudine therapy results in HBeAg response rates that are similar to those obtained with a standard course of IFN alpha [Schlam 2000]. Results are similar in Asians and Caucasians [Dienstag et al., in press]. Importantly, rates are highest in patients with elevated levels of ALT, i.e., those with active liver disease (Fig. 2), possibly reflecting an association between disease severity, HBV replication and susceptibility to the action of lamivudine. Further results from 2- and 3-year studies of lamivudine therapy show that the cumulative HBeAg seroconversion rate continues to increase with extended therapy [Liaw et al., 1998; Leung et al., 1999]. In the Asian study, 65% of patients with a baseline ALT of greater than or equal to 2× the upper limit of normal (ULN) demonstrated HBeAg seroconversion within 3 years of initiating lamivudine therapy [Chang et al., 1999].

Data from uncontrolled trials also suggest that lamivudine is useful for the treatment of patients with decompensated liver disease. As in patients with more moderate disease, lamivudine markedly suppresses viral replication and often stabilises or improves markers of liver disease in this patient group [Van Thiel et al., 1997]. Some patients with advanced disease, however, may not benefit from lamivudine because of pre-existing irreversible progression of their disease to a

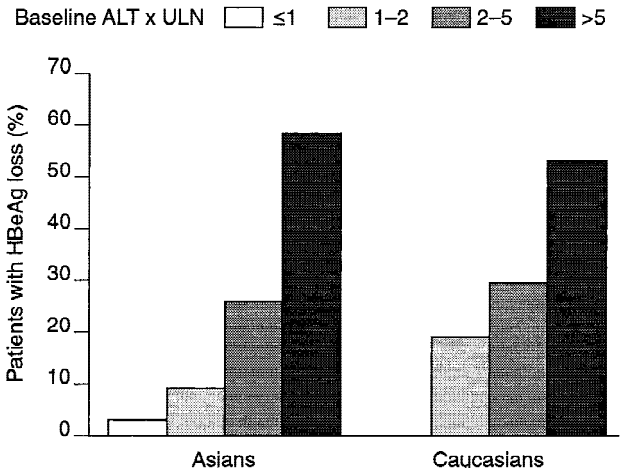

Fig. 2. The effect of baseline alanine amino transferase (ALT) and ethnicity on hepatitis B e antigen (HBeAg) loss. Composite data from Phase III studies of 1 year of lamivudine therapy. ULN, upper limit of normal. Reproduced with permission.

terminal state. Follow-up of patients who have seroconverted shows that most patients maintain their serological status at 12 months' post-treatment [Schiff et al., 1998b]. Results from Phase III trials with lamivudine show that 86% (36/42) of patients continue to be HBeAg-negative and that 79% (23/29) maintain normal serum ALT concentrations at 1 year (Fig. 3) [Schiff et al., 1998b].

LAMIVUDINE IMPROVES LIVER DISEASE AND HISTOLOGY

Phase III trials have shown that lamivudine normalises serum ALT within 6–12 months (Fig. 4). This improvement in ALT is also reflected in histological improvement. In three studies, improvements in liver histology have been greater in patients who have received lamivudine than in those who have received placebo [Dienstag et al., 1998, 1999; Lai et al., 1998; Schiff

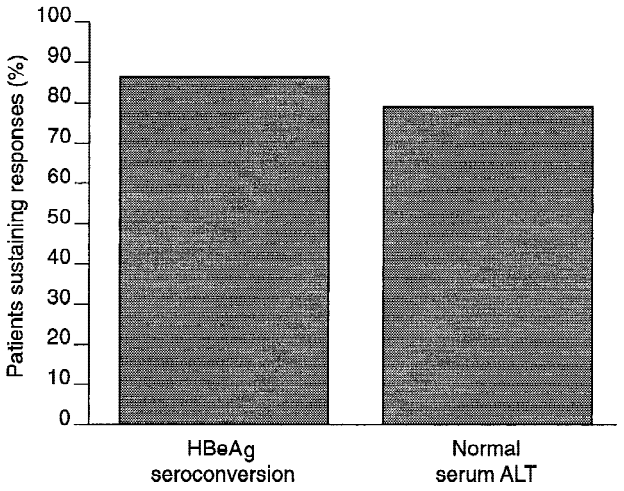

Fig. 3. Responses to lamivudine therapy at 12-month median follow-up. (**a**) Hepatitis B e antigen (HBeAg) seroconversion; (**b**) serum alanine amino transferase (ALT).

et al., 1998a]. There was a beneficial effect on liver disease for two-thirds of the patients receiving lamivudine. Improvements in ALT or liver histology occurred in many patients, even in the absence of HBeAg seroconversion. Further evidence from studies that were not placebo controlled shows improved liver histology in most lamivudine-treated patients [Schlam et al., 2000; Tassopoulos et al., 1999a].

Lamivudine reduces necro-inflammation and, hence, should also reduce progression of fibrosis. Patients followed for 12 months after lamivudine treatment show a marked reduction in progression of fibrosis [Dienstag et al., 1998; Lai et al., 1998; Schiff et al., 1998a] and in progression to cirrhosis (1.8% for lamivudine vs. 7% for placebo; $P = 0.04$) [Goodman et al., 1999].

SAFETY PROFILE OF LAMIVUDINE

Lamivudine is well tolerated and has a safety profile similar to that of placebo during treatment. The safety of lamivudine for the treatment of patients with noncompensated chronic hepatitis B has been established from data on 967 patients in four international, multicentre, controlled Phase III trials [Dienstag et al., 1998; Schlam et al., 2000; Lai et al., 1998; Schiff et al., 1998a]. In these trials, 558 patients received lamivudine at 100 mg/day. During treatment, the incidence of adverse events was similar in those receiving either lamivudine or placebo (Table I). [Leung et al., 1998]. Patient age, sex, presumed route of infection and the presence or absence of cirrhosis had no influence on the incidence of adverse reactions. Liver enzyme elevations and haematological toxicity did not differ significantly in patients receiving lamivudine or placebo.

By contrast, a comparison of lamivudine with IFN alpha treatment showed that the incidence of drug-related adverse events was markedly lower with lamivudine monotherapy compared with patients receiving IFN alpha treatment [Schalm et al., in press]. Typical flu-like side effects occurred in about two-thirds of the IFN alpha recipients (Table II) [Leung et al., 1998]. Combination therapy with lamivudine and IFN alpha produced an adverse event profile that was similar to that of IFN alpha alone.

Treatment with IFN alpha is sometimes associated with significant increases in serum ALT, that are potentially hazardous [Perrillo, 1994; Marinos et al., 1994; Gaeta et al., 1995; Hassanein et al., 1996; Hoofnagle and Di Bisceglie, 1997]. In contrast, lamivudine was associated with only modest ALT elevations during treatment. These were generally asymptomatic and self-limiting. Clinically significant post-treatment events (i.e., ALT elevations with an accompanying increase in bilirubin) were uncommon with lamivudine and occurred at a frequency (1%) similar to that seen in patients receiving placebo [Leung et al., 1998]. Therefore, although post-treatment ALT elevations are noted more frequently after lamivudine therapy than after placebo, there is no evidence for an increased incidence of hepatic decompensation in these patients. Finally, lamivudine has no clinically significant interactions with other drugs [Johnson et al., 1999].

LAMIVUDINE EFFICACY AFTER EMERGENCE OF YMDD VARIANTS

HBV variants with mutations in the YMDD motif (tyrosine-methionine-aspartate-aspartate) have emerged during extended treatment with lamivudine [Atkins et al., 1998]. These variants, however, are less replication-competent than the wild-type virus [Melegari et al., 1998] and become detectable only after the 'fitter' wild-type viruses have been suppressed by lamivudine. The less replication-competent YMDD variants produce a lesser viraemia than would be the case in the absence of treatment.

Prediction of the appearance of YMDD variants in an individual patient before treatment with lamivudine is not possible. Monitoring of serological status can usually identify those who may have developed YMDD variants. If after 24 weeks of therapy with lamivudine the patient remains HBeAg-positive, ALT remains higher than 1.3× the ULN and HBV DNA is still present, there is a 99% chance that YMDD variants are present [Atkins et al., 1998].

The prevalence and clinical correlates of YMDD variants have been determined in 967 patients from Phase III studies with lamivudine [Atkins et al., 1998]. This analysis showed that YMDD variants seldom occur during the first 36 weeks of therapy, but that prevalence increases with more prolonged therapy (1 year, 24%; 3 years, 49%) [Atkins et al., 1998; Leung et al., 1999]. Emergence is positively associated with baseline HBV DNA, the histological activity index (HAI) and the body-mass index. Paradoxically, the first two factors also predispose patients to HBeAg seroconversion, and are important indicators of a need for therapeutic intervention.

The management of patients with YMDD variants is challenging. Clinical relapse may occur in individuals

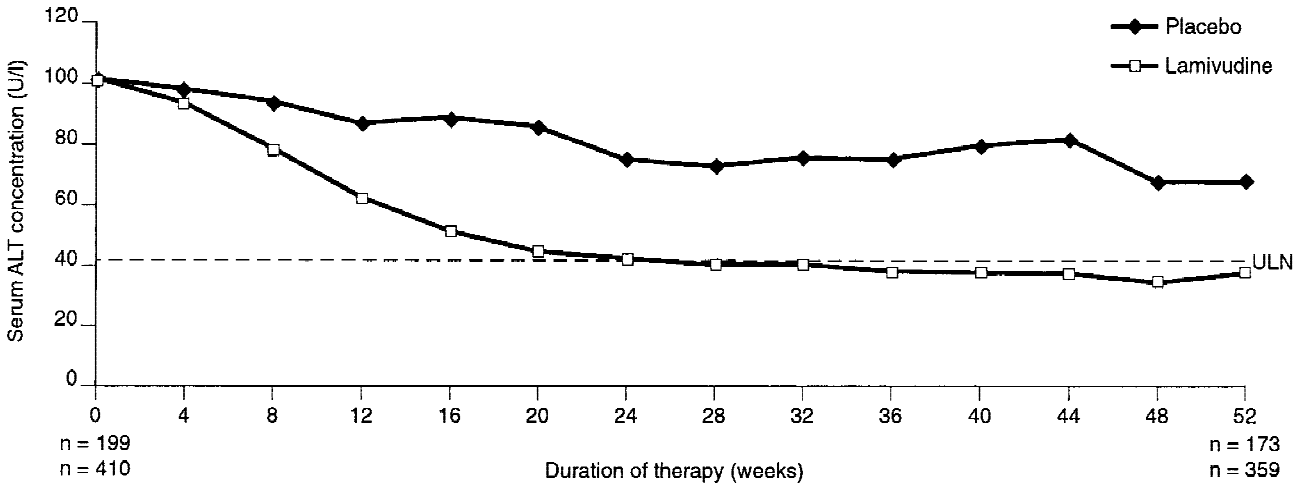

Fig. 4. Improvement in serum alanine amino transferase (ALT) during treatment with lamivudine—composite data from Phase III clinical trials. Adapted from Zeffix™ Lamivudine Product Monograph. GlaxoWellcome, 1999.

TABLE I. Percentage of Patients With Adverse Events in Patients Receiving Lamivudine or Placebo

Adverse event	Lamivudine (n = 416)	Placebo (n = 200)
Malaise and fatigue	26	28
Headache	22	21
Viral respiratory infection	19	17
Nausea and vomiting	16	17
Abdominal discomfort/pain	15	17
Ear/nose/throat infections	14	12
Diarrhoea	14	12
Viral ear/nose/throat infections	11	11
Throat and tonsil discomfort/pain	11	8
Cough	10	9
Musculoskeletal pain	8	10

Composite data from Phase III clinical trials. Adapted from Zeffix™ Lamivudine Product Monograph. Glaxo Wellcome, 1999.

TABLE II. Percentage of Patients With Adverse Events in Patients Receiving Lamivudine or IFN Alpha

Adverse event	Lamivudine (n = 416)	IFN alpha (n = 70)
Malaise and fatigue	26	70
Headache	22	47
Viral respiratory infection	19	37
Nausea and vomiting	16	34
Muscle pain	8	40
Temperature disturbance	7	43
Arthralgia	6	23
Depression	4	13
Feeding problems	3	33
Hair loss	3	23
Decreased white cells	1	26

Composite data from Phase III clinical trials. Adapted from Zeffix™ Lamivudine Product Monograph. Glaxo Wellcome, 1999.

who develop a significant population of YMDD variants during treatment. In most patients with YMDD variants, however, serum ALT and HBV DNA remain below baseline values as long as lamivudine therapy is continued. On an individual basis, it is important to differentiate this picture from that due to non-compliance, i.e., that will tend to generate similar results. In the minority of patients who do not seroconvert and who develop the YMDD variant during treatment, continuation of lamivudine treatment is recommended to maintain suppression of the wild-type HBV and hence reduce the likelihood of the progression of liver disease [Yao, 1999]. If lamivudine treatment is stopped then the wild-type virus will return and ALT levels increase further. Most patients who have been treated with lamivudine for 3 years, and have had the variant for 2 or more years, have ALT concentrations that remain below baseline measurements [Leung et al., 1999]. Thus, despite the emergence of YMDD variants, lamivudine still results in improvements in serum ALT, liver histology and HBV DNA levels that may persist long term. The clinical benefits of lamivudine are, however, greatest for those who achieve HBeAg seroconversion or who remain free of YMDD variants despite not gaining seroconversion [Leung et al., 1999].

RECOMMENDATIONS FOR TREATMENT WITH LAMIVUDINE

Phase III trials have established the safety and efficacy of lamivudine. In addition, they provide the basis for developing guidelines for use in clinical practice. Patient selection should be based upon establishing a diagnosis of chronic liver disease due to persistent HBV replication. The virological criteria can be met on the basis of positive tests for hepatitis B surface antigen (HBsAg) and either HBeAg or HBV DNA. An elevated ALT is evidence of active liver disease, and a liver biopsy can provide more detailed information of liver disease status. Patient selection is not influenced by factors such as age, ethnicity, hepatic function, prior IFN alpha therapy, or the presence of pre-core mutant HBV [Dienstag et al., 1999; Lai et al., 1998; Schiff et al., 1998a; Tassopoulos et al., 1999a, 1999b; Yao et al., in press]. Lamivudine is also effective at

suppressing HBV replication both before and after liver transplantation [Grellier et al., 1996; Perrillo et al., 1997a, 1997b], and provides clinical benefit to those with liver decompensation [Sponseller et al., 1998; Van Thiel et al., 1997; Villeneuve et al., 1997].

The optimal duration of therapy is influenced by a patient's disease status and the aim of treatment. Data indicate that improvements in liver disease generally persist after treatment with lamivudine when therapy has been maintained until the patient showed sustained loss of HBeAg or HBeAg seroconversion. During treatment, patients can generally be managed by periodic assessment of ALT and HBeAg, and other liver function tests if necessary. Likewise, the management of patients after the emergence of YMDD variant HBV may be influenced by disease status and treatment objectives. Ongoing studies may help to define how to optimise therapy in patients, both with and without variants.

CONCLUSIONS

Lamivudine is the first effective treatment for chronic hepatitis B patients with viral replication and liver disease. It is a potent, once-daily, oral antiviral therapy that has been proven to be both effective and well tolerated in comparison with placebo and with IFN alpha therapy. Treatment with lamivudine suppresses viral replication (serum HBV DNA and HBeAg levels), enhances HBeAg seroconversion, normalises liver necro-inflammatory disease (as measured by ALT levels and liver histology) and reduces progression to cirrhosis. YMDD variant HBV may emerge with prolonged therapy but, with continued therapy with lamivudine, control of the disease is generally maintained.

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