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Lamivudine

A Review of its Therapeutic Potential in Chronic Hepatitis B

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Data Selection

Sources: Medical literature published in any language since 1966 on lamivudine, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase, Medline and EMBASE search terms were 'lamivudine', '2-3-dideoxy-3-thiacytidine', '3-TC', '3TC', 'BCH-189', 'BCH-790', 'BTC', 'GR-103665', 'GR-109714', 'GR-109714X', 'NGPB-21', 'SDDC' and 'hepatitis-B'. Searches were last updated 31 May 1999.

Selection: Studies in patients with hepatitis B who received lamivudine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Hepatitis B, lamivudine, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Lamivudine is a deoxycytidine analogue that is active against hepatitis B virus (HBV). In patients with chronic hepatitis B, lamivudine profoundly suppresses HBV replication.

Clinically significant improvements in liver histology and biochemical parameters were obtained with lamivudine in double-blind, randomised, trials in hepatitis B e antigen (HBeAg)-positive patients with chronic hepatitis B and compensated liver disease. After 52 weeks of treatment, relative to placebo (≤25%), significantly more Chinese (56%) or Western patients (52%) treated with lamivudine 100 mg/day had reductions of ≥2 or more points in Knodell necroinflammatory scores. Moreover, significantly fewer lamivudine 100 mg/day than placebo recipients had progressive fibrosis in liver biopsies (≤5 *vs* ≥15%) and fewer lamivudine- than placebo-treated patients progressed to cirrhosis (1.8 *vs* 7.1%). More lamivudine 100 mg/day than placebo recipients acquired antibodies to HBeAg after 52 weeks (16 *vs* 4% in Chinese patients and 17 *vs* 6% in Western patients). ALT levels normalised in significantly more lamivudine than placebo recipients enrolled in these trials.

In HBeAg-negative, HBV DNA positive patients with compensated liver disease enrolled in a double-blind, randomised study, HBV DNA levels were suppressed to below the limit of detection (< 2.5 pg/ml) and ALT levels normalised in 63% and 6% of patients treated with lamivudine 100 mg/day or placebo for 24 weeks. Clinically significant improvements in liver histology were obtained in 60% of patients treated with lamivudine for 52 weeks in this study.

Lamivudine 100 mg/day for 52 weeks produced similar or significantly greater improvements in liver histology and ALT levels than 24 weeks' treatment with lamivudine plus interferon-α.

In liver transplant candidates with chronic hepatitis B and end-stage liver disease, lamivudine 100 mg/day alone, or in combination with hepatitis B immune globulin, generally suppressed HBV replication and appeared to protect the grafted liver from reinfection. Lamivudine 100 mg/day suppressed viral replication and improved liver histology in liver transplant recipients with recurrent or *de novo* chronic hepatitis B. Lamivudine 300 or 600 mg/day reduced HBV replication in HIV-positive patients.

The incidence of adverse events in patients with chronic hepatitis B and compensated liver disease treated with lamivudine 100 mg/day or placebo for 52 to

68 weeks was similar. 3.1- to 10-fold increases in ALT over baseline occurred in 13% of patients during treatment with lamivudine 100 mg/day or placebo for 52 weeks. Post-treatment ALT elevations were more common in lamivudine than placebo recipients; however, these generally resolved spontaneously; ≤1.5% of lamivudine- or placebo-treated patients experienced hepatic decompensation.

Conclusion: Lamivudine inhibits HBV replication, reduces hepatic necroinflammatory activity and the progression of fibrosis in patients with chronic hepatitis B, ongoing viral replication and compensated liver disease including HBeAg-negative patients. The drug also suppresses viral replication in liver transplant recipients and HIV-positive patients. Thus, lamivudine is potentially useful in a wide range of patients with chronic hepatitis B and ongoing viral replication.

Pharmacodynamic Properties

Lamivudine is a deoxycytidine analogue with antiviral properties. Lamivudine is phosphorylated by host cell kinases to a triphosphate moiety that is active against hepatitis B virus (HBV). The concentration of lamivudine required to reduce HBV DNA concentrations by 50% (EC_{50}) and 90% (EC_{90}) in the supernatant of cultures of human hepatocellular carcinoma cell lines (2.2.15 and HB611 cells) was 0.008 to 0.1 μmol/L and 0.16 to 0.9 μmol/L, respectively. EC_{50} and EC_{90} values for lamivudine were 2.7- to 5.75-fold lower than those for penciclovir (the active metabolite of famciclovir).

Lamivudine significantly suppressed HBV replication in a chimaeric mouse-human model of chronic hepatitis B infection. After 4 days of treatment with lamivudine 0.5mg twice daily, mean HBV DNA levels were reduced by 97% and only 14% of mice had detectable HBV DNA levels [limit of detection (LOD) < 5×10^3 copies/ml]. In contrast 90% of control mice had detectable HBV DNA levels. HBV DNA levels increased substantially within 5 days of the cessation of treatment.

Lamivudine-resistant HBV has been isolated from some patients with chronic hepatitis B during treatment with lamivudine. In lamivudine-resistant clinical isolates a point mutation in a highly conserved motif [Tyr-Met-Asp-Asp (YMDD)], in which valine (M552V) or isoleucine (M552I) is substituted for methionine, has been consistently identified. A second mutation (L528M), in which methionine replaces leucine 24 amino acids upstream, has been identified in some isolates containing M552V and M552I and confers cross-resistance to famciclovir. Lamivudine-resistant HBV does not appear to be cross-resistant to adefovir. The EC_{50} of 1 clinical isolate increased 45-fold after acquiring M552V. In addition, the EC_{50} of lamivudine in HepG2 cells transfected with viral constructs containing M552V was 153-, 550- and 3010-fold greater for HBV containing M552V, M552I and L528M plus M552V, respectively, than for that containing wild-type HBV. Clinical observations suggest that replication is slower in HBV with YMDD variant motifs than in wild-type virus.

Four and 14% of 285 Chinese patients, respectively, acquired resistant YMDD variant genotypes after 9 and 12 months of lamivudine therapy. However, histological responses were not affected by the presence of YMDD variant HBV.

Lamivudine does not interfere with human DNA synthesis and exhibits little cytotoxicity in human cell lines. The 3′-5′ exonuclease function of human DNA polymerase γ (mitochondrial DNA polymerase) excised lamivudine 5′-monophosphate incorporated during chain termination assays and lamivudine (0.01 to 0.03 μmol/L) did not appreciably inhibit DNA synthesis in intact mitochondria. Moreover, no morphological or functional changes in hepatocellular mitochon-

dria were detected in liver biopsy specimens from patients treated with lamivudine 25 to 300 mg/day.

Cellular immune responsiveness increased during treatment with lamivudine in patients with chronic hepatitis B. Statistically significant increases in proliferation of T cells obtained from 12 patients with chronic hepatitis B occurred during treatment with lamivudine 100 mg/day and were associated with suppression of HBV DNA levels.

Pharmacokinetic Properties

Lamivudine is well absorbed after oral administration (mean bioavailability 86 to 88%). The drug is not extensively bound to plasma proteins (36%), distributes into total body fluid (volume of distribution 1.3 L/kg) and crosses the placenta (the drug is present in amniotic fluid), where concentrations appear to equilibrate between the maternal and foetal circulation.

In 6 patients with chronic hepatitis B receiving lamivudine 100 mg/day, the mean maximum plasma concentration (C_{max}) of lamivudine at steady state was 1.1 mg/L, the mean area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{24}) was 4.72 mg/L • h and the mean terminal elimination half-life was 6.2 hours. In paediatric patients (2 to 12 years of age) with chronic hepatitis B, lamivudine 3 mg/kg once daily provided a steady state C_{max} and AUC of ≈1.5 mg/L and ≥4 mg/L • h.

The major route of elimination of lamivudine is renal excretion. In patients with moderate/severe renal dysfunction [i.e. those with creatinine clearance <3 L/hr (<50 ml/min)] elimination of lamivudine is significantly retarded and the dosage should be adjusted. Dosage modifications are not required in patients with decompensated liver disease.

Therapeutic Potential in Chronic Hepatitis B

Lamivudine has been evaluated in randomised, placebo-controlled studies in immunocompetent patients with chronic hepatitis B and compensated liver disease, including HBeAg-negative, HBV DNA-positive patients. The drug has also been studied in HBV DNA-positive liver transplant candidates with chronic hepatitis B. The effect of lamivudine in HIV-positive patients with chronic hepatitis B has been described. Histological improvement in liver biopsy specimens was the primary or secondary end-point in several studies. Markers of hepatitis B replication, hepatitis B serology, and normalisation of ALT levels were also used as end-points in these studies.

The results of dose ranging studies with lamivudine in patients with chronic hepatitis B and compensated liver disease suggest that daily dosages ≥100 mg/day are optimal for this indication.

Clinically significant improvements in liver histology were obtained with lamivudine in 2 double-blind, randomised trials in HBeAg-positive immunocompetent patients with chronic hepatitis B and compensated liver disease. Significantly more Chinese (56%) or Western patients (52%) treated with lamivudine 100 mg/day than placebo recipients (≤25%) had clinically significant reductions (defined as a reduction of ≥ 2 points) in Knodell necroinflammatory scores after 52 weeks of treatment. Worsening fibrosis was detected in ≥15% of placebo recipients, but in ≤ 5% of lamivudine 100 mg/day recipients during these 2 studies.

Significantly more lamivudine 100 mg/day than placebo recipients converted from HBeAg-positive to positive for antibodies to HBeAg (anti-HBe) during 52 weeks of treatment in these 2 studies (16 *vs* 4% in Chinese patients and 17 *vs* 6% in Western patients). Among Chinese patients randomised to further double-blind

treatment with lamivudine 100 mg/day, the proportion of patients who seroconverted from HBeAg-positive to anti-HBe was 27% and 33%, respectively, after 2 and 3 years.

Lamivudine generally reduced ALT levels in patients enrolled in these trials. In Chinese patients in whom ALT levels were elevated at baseline, normalisation of ALT levels occurred in 72% of those treated with lamivudine 100 mg/day, but in only 24% of placebo recipients. Similarly, ALT normalisation was more common in Western patients treated with lamivudine 100 mg/day or placebo for 52 weeks (41 *vs* 7%).

Lamivudine 100 mg/day reduced HBV DNA, HBeAg and ALT levels and produced improvements in liver histology in Japanese patients with chronic hepatitis B.

Lamivudine was generally effective in suppressing HBV replication and ameliorating liver disease in HBeAg-negative patients (presumed to harbour precore mutant HBV) with chronic hepatitis B and compensated liver disease. Significantly more patients treated with lamivudine 100 mg/day in a randomised double-blind study achieved the primary efficacy end-point, HBV DNA levels < 2.5 pg/ml and ALT levels within the normal range, than placebo-treated patients after 24 weeks (63 *vs* 6%). Of patients enrolled in this trial who had evaluable liver biopsies at baseline and after 52 weeks of treatment with lamivudine 100 mg/day, 60% had a reduction of ≥2 or more points in the Knodell necroinflammatory score. These results show that the effectiveness of lamivudine in HBeAg-negative patients with chronic hepatitis B is generally similar to that in HBeAg-positive patients.

Histological responses were reported in 2 studies in which patients with chronic hepatitis B and compensated liver disease received lamivudine 100 mg/day alone for 52 weeks or combined with interferon-α 30 million units (MU) per week for 16 weeks. However, liver biopsies were obtained at the end of treatment with lamivudine and 28 or 36 weeks after completion of therapy with lamivudine plus interferon-α or interferon-α monotherapy, which makes interpretation of the results difficult. Among patients receiving lamivudine monotherapy for 52 weeks in these 2 studies, 52 and 38% of patients had clinically significant reductions in Knodell necroinflammatory scores. In 1 study, in which only patients refractory to interferon-α were enrolled, a significantly greater proportion of patients treated with lamivudine 100 mg/day experienced clinically significant improvement in liver histology at 52 weeks than those treated with lamivudine 100 mg/day alone for 8 weeks and then combined with interferon-α for 16 weeks.

A pooled analysis of 3 clinical trials revealed the frequency of progression to cirrhosis to be 1.8, 7.1 and 9.5%, respectively, after 1 year of treatment with lamivudine 100 mg/day, placebo and interferon-α.

Lamivudine 150 mg/day plus interferon-α 13.5 MU/week was more effective than ganciclovir 750 mg/day plus interferon-α 13.5 MU/week in suppressing HBV replication during a 26-week study. HBV DNA levels rebounded after discontinuation of antiviral therapy.

Lamivudine 100 mg/day was more effective than famciclovir 500mg 3 times daily in suppressing HBV replication in patients with chronic hepatitis B. 78% of lamivudine recipients, but only 8% of famciclovir recipients experienced a

reduction of >2 $\log_{10}$ in HBV DNA levels or were HBV DNA negative (LOD ≤2.5 pg/ml) after 12 weeks' of treatment ($p < 0.0001$).

When started before transplantation, lamivudine 100 or 150 mg/day suppressed HBV DNA levels in most liver transplant candidates with chronic hepatitis B and end-stage liver disease. Hepatitis B core antigen (HBcAg) was not detected in biopsy specimens obtained from ≥50% of patients after transplantation in 4 small studies (n = 4 to 38). Most patients were hepatitis B surface antigen- and HBeAg-negative after transplantation.

No evidence of hepatitis B replication (e.g. HBV DNA or HBeAg in serum) was evident in liver transplant recipients treated with lamivudine 100 mg/day before transplantation and lamivudine 100 mg/day plus hepatitis B immune globulin (HBIg) during and after transplantation.

In 52 liver transplant recipients with recurrent or *de novo* chronic hepatitis B, lamivudine 100 mg/day for 52 weeks suppressed HBV DNA below the LOD (≤1.6 pg/ml) in 60% of patients and improved liver histology in 51% of patients. YMDD variant HBV was detected in 14 patients, 5 of whom experienced clinical deterioration due to the progression of hepatic disease.

Lamivudine was effective in reducing HBV DNA replication in HIV-positive patients with chronic hepatitis B. In 30 patients with high rates of HBV replication (HBV DNA >5 ng/L and HBeAg-positive) prior to treatment only 15% (4 of 27) remained HBV DNA-positive (by PCR) after 52 weeks of lamivudine 300 or 600 mg/day. Similarly, none of 10 patients with low rates of HBV DNA replication (HBV DNA <5 ng/L and HBeAg-negative) were HBV DNA-positive at the end of treatment compared with 6 at baseline. A retrospective analysis showed 27 of 66 (41%) HBV DNA-positive patients became HBV DNA-negative (assay not described) during treatment with lamivudine 300 mg/day for HIV infection compared with 3 of 17 (18%) placebo recipients.

In children aged 2 to 12 years with chronic hepatitis B, lamivudine oral solution 3 mg/kg/day (approximately twice the dosage used in adults with chronic hepatitis B) produced maximal antiviral effects (99.9% inhibition of viral replication).

Tolerability

The incidence of adverse events in lamivudine- or placebo-treated patients was similar in a pooled analysis of 4 randomised, double-blind trials in patients with hepatitis B. One or more drug-related adverse events were reported by 40 and 45% of patients, respectively, treated with lamivudine 100 mg/day (n = 416) or placebo (n = 200) for 52 to 68 weeks in these trials. ALT levels increased by ≥3.1-fold over baseline in 13% of patients during treatment with lamivudine 100 mg/day or placebo for 52 weeks.

Lamivudine was better tolerated than interferon-α in comparative trials. The frequency of malaise and fatigue, fever and chills, muscle pain, nausea and vomiting, hair loss or depressive disorders was 2 to 8 times more common in patients treated with interferon-α, alone or in combination with lamivudine, than lamivudine 100 mg/day.

Substantial elevations in ALT levels have occurred during treatment and follow-up in patients receiving lamivudine or placebo in randomised trials. Although ALT elevations were more common in lamivudine- than placebo-treated patients after discontinuation of treatment, ALT elevations generally resolved spontaneously and the incidence of hepatic decompensation was rare (i.e. ≤1.5%) in both groups.

Dosage and Administration

Lamivudine 100mg given once daily is the recommended dosage in HIV-negative patients with chronic hepatitis B, ongoing viral replication and compensated liver disease. In HIV-positive patients the dosage is 150mg twice daily in combination with other antiretroviral agents. The drug may be taken with or without food. Dosage adjustments are recommended in patients with chronic hepatitis B and clinically significant renal dysfunction.

1. Chronic Hepatitis B

Hepatitis B virus (HBV) is a small partially double-stranded DNA virus of the family hepadnaviridae. After entering a host liver cell, the relaxed circular DNA of the virus is translocated to the nucleus and converted to covalently closed circular DNA which serves as an episomal template for RNA production (fig. 1).[1] The resulting messenger RNA transcripts, in turn, serve as templates for reverse transcription of DNA for inclusion in infectious virions. As in retroviruses, reverse transcription is an essential step in the life cycle of HBV; however, unlike retroviruses, integration of HBV DNA into the host cell genome is not required for replication.[2] Nonetheless, HBV may become integrated into host cell DNA,[3] and this may be a prerequisite for HBV-induced hepatocellular carcinogenesis.[4-6]

Cells infected with HBV produce several viral antigens.[7] Hepatitis B surface antigen (HBsAg) is secreted in large quantities (fig. 2), both as a component of infectious virions and as empty noninfectious subviral particles.[1] The presence of hepatitis B e antigen (HBeAg) in serum indicates high levels of virus replication. However, the absence of HBeAg in serum does not automatically imply a nonreplicative state, since precore mutants, which lack HBeAg, are well known.[8,9] Hepatitis B core antigen (HBcAg) is found only in liver cells and antibodies to HBcAg (anti-HBc), which arise early in the course of infection, are detectable in all patients exposed to HBV.[7,10]

Detection of HBV DNA in serum also indicates high levels of virus replication.[9] HBV is not intrinsically hepatotoxic in immunocompetent individuals; rather, liver injury results from a cellular immune response directed at viral proteins, most likely HBcAg and HBeAg.[7,8,10]

Hepatitis B infection is immunologically cleared in more than 90% of adult patients who acquire the virus by exposure to infected blood or body fluids (e.g. through sexual contact, intravenous drug use, occupational exposure or blood transfusion), which is the most important mode of transmission in Western countries.[10] In contrast, after perinatal transmission of HBV, which is common in Asian and African nations, 95% of individuals remain chronically infected, presumably because of the development of immune tolerance.[10,11]

Chronic hepatitis B is defined as the presence of HBsAg or other viral markers in serum for more than 6 months.[12] Individuals with chronic hepatitis B have a high risk of developing cirrhosis, liver failure and hepatocellular carcinoma.

The dynamics of HBV infection in patients with chronic hepatitis B have been modeled. At steady state more than 10^{11} virus particles enter the circulation from infected cells each day,[13,14] and the daily turnover of free virus in serum is approximately 50%.[13] The half-life of virus in serum has been estimated to be less than 3 days.[13,14] Divergent estimates of the half-life of an infected liver cell have been published: mean half-lives of 13 (range 10 to 100)[13] and more than 100 days[14] have been calculated. If, for example, the half-life of an infected hepatocyte was 100 days, then complete suppression of HBV replication for 12 months with an antiviral agent such as lamivudine would reduce the number of infected cells to approximately 8% of the original population.[13] Hence, prolonged treatment with antiviral agents may be required to eradicate HBV in patients with chronic hepatitis B.

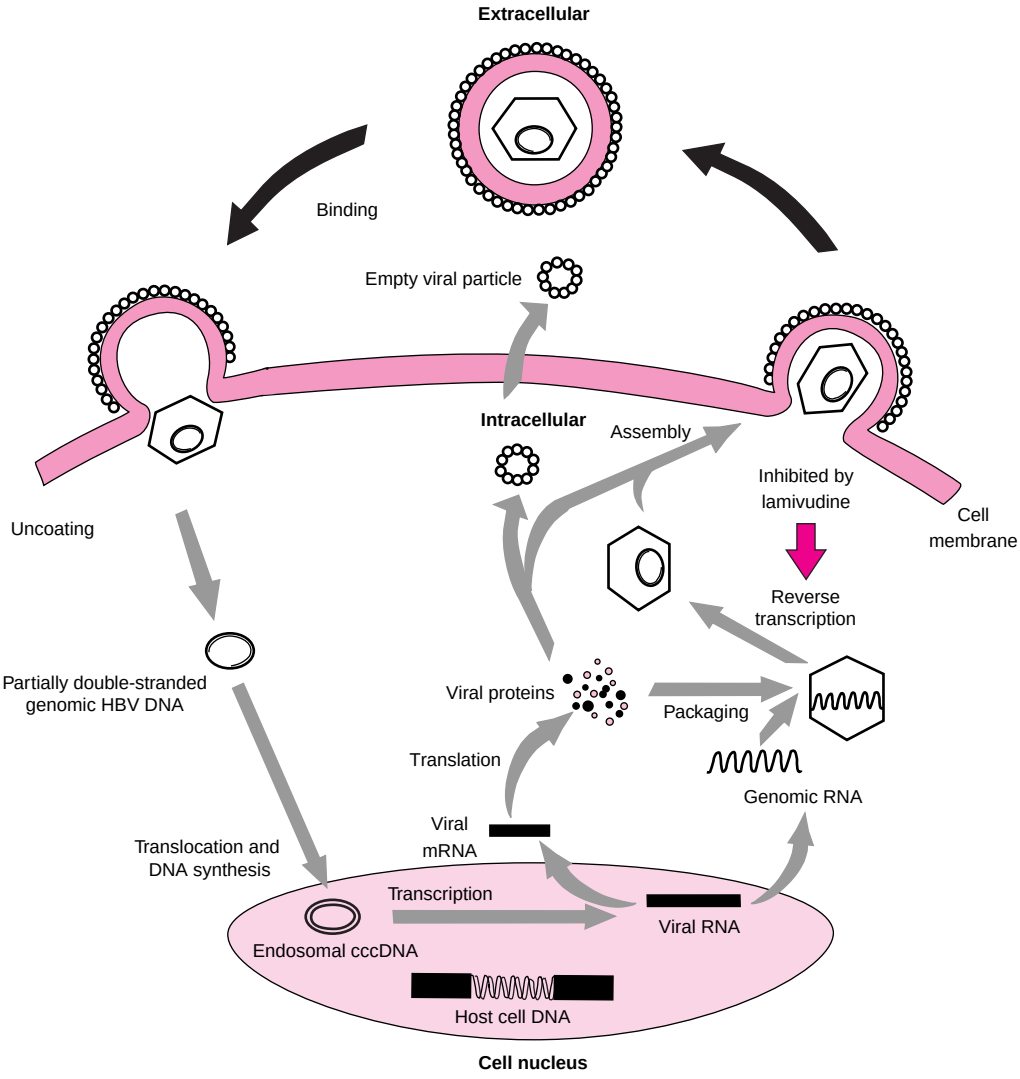

Fig. 1. The replication cycle of hepatitis B virus (HBV) and the site of action of lamivudine. Integration of HBV DNA into the host cell genome and the intracellular amplification of HBV DNA are not depicted in the figure. **cccDNA** = covalently closed circular DNA; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen.

Interferon-α is an approved therapy for chronic hepatitis B. However, this agent is effective only in a subset of patients, is often poorly tolerated, requires parenteral administration and is expensive (section 7). Hence, there is a need for alternative therapies for chronic hepatitis B. Lamivudine is a deoxycytidine analogue with an L configuration that has antiviral properties and a well-established role in the treatment of HIV infection.[15] This article reviews the use of lamivudine in patients with chronic hepatitis B.

2. Pharmacodynamic Properties

After uptake by infected cells, lamivudine is sequentially phosphorylated by deoxycytidine kinase and pyrimidine nucleotide kinases of the host

cell to form lamivudine triphosphate, the antiviral moiety which inhibits HBV polymerase and the reverse transcriptase of HIV (fig. 3).[15-18] Lamivudine triphosphate lacks a 3′ hydroxyl group and causes the termination of chain elongation when incorporated into nascent DNA transcripts during reverse transcription. In contrast, the drug does not interfere with transcription of HBV DNA integrated into host cell DNA.[20] In a human hepatoma cell line (2.2.15) the intracellular half-life of lamivudine triphosphate was 17 to 19 hours (reviewed in Johnson et al.[19]).

2.1 Antiviral Activity Against Hepatitis B Virus

2.1.1 In Vitro *Activity*

Lamivudine has been studied in an HBV DNA-producing human hepatocellular carcinoma cell line (2.2.15 cells) that is considered to be an accurate model of chronic HBV viral replication. Lamivudine 0.008 to 0.1 μmol/L reduced supernatant HBV DNA levels by 50% (EC_{50}; in 2.2.15 and HB611 cells).[21-28] The concentration of lamivudine required to reduce HBV DNA levels by 90% (EC_{90}) ranged from 0.16 to 0.9 μmol/L in 2.2.15 cells.[21,23,26-28] The concentration of intracellular HBV DNA replication intermediates in 2.2.15 cells was reduced by 50% after incubation with lamivudine 0.08[23] or 0.2[21] μmol/L and by 90% after incubation with lamivudine 0.3[23] or 0.6[21] μmol/L. Moreover, EC_{50} and EC_{90} values for lamivudine were 2.7- to 5.75-fold lower than those for penciclovir in 2.2.15 cells (fig. 4).[21,27]

Lamivudine enhanced the *in vitro* activity of penciclovir or interferon-α against HBV. Lamivudine plus interferon-α (3000 or 10 000 IU/ml interferon-α : 1 μmol/l lamivudine) or penciclovir (in a 3 : 1 or 10 : 1 ratio of penciclovir to lamivudine) decreased HBV DNA production to a greater extent than penciclovir or interferon-α alone in 2.2.15 cells.[29] Phosphorylation of lamivudine was significantly increased when 2.2.15 cells were incubated with fludarabine (5 μmol/l) or thymidine (20, 50 or 100 μmol/l), presumably by modulation of deoxycytidine kinase activity.[18] Similarly, phosphorylation of lamivudine in a T-lymphoblastoid cell line (CEM) was enhanced by incubation with hydroxyurea (1 mmol/l), fludarabine (5 μmol/l) or thymidine (100 μmol/l).[16,18]

2.1.2 In Vivo *Activity in Hepatitis B Virus-Trimera Mice*

A chimaeric mouse-human model has recently been developed which simulates chronic hepatitis B. After total body irradiation, normal mice were engrafted with bone marrow from mice with severe

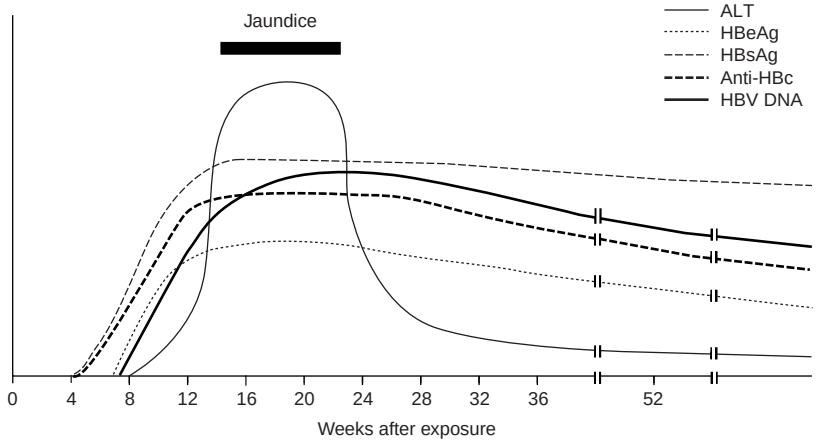

Fig. 2. Serological markers of chronic hepatitis B in a recently infected person. ALT levels may be normal or elevated in patients with chronic hepatitis B. HBeAg is not present in the serum of patients infected with precore mutants. **Anti-HBc** = antibodies against hepatitis B core antigen; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV DNA** = hepatitis B virus DNA.

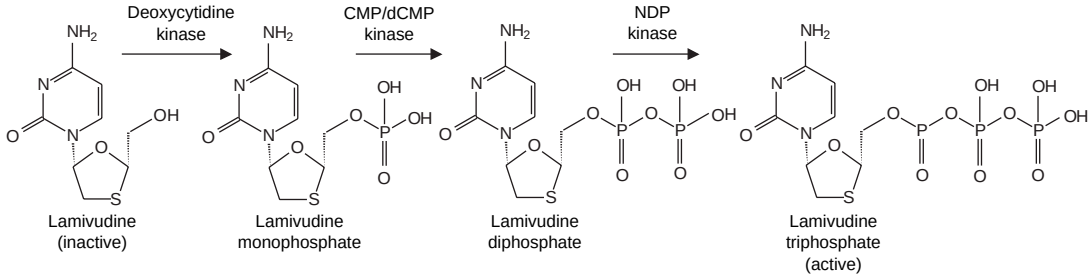

Fig. 3. Intracellular phosphorylation of lamivudine. **CMP** = cytidine monophosphate; **dCMP** = deoxycytidine monophosphate; **NDP** = nucleoside diphosphate. Adapted from Johnson et al.[19] with permission.

combined immunodeficiency disease (SCID) to produce a mouse permissive for engraftment of human tissue. Next, fragments of HBV-infected human liver were transplanted into these mice to produce an animal comprised of 3 genetically distinct tissues (hence 'trimera'). HBV DNA levels typically reach a peak within 18 to 25 days after introduction of the human liver explant into the host mouse.[30]

Lamivudine suppressed HBV replication in trimera mice. The mice were treated with intraperitoneal lamivudine 0.5mg twice daily between days 12 and 15 after liver transplantation (i.e. each mouse received 4mg lamivudine). On day 16, 90% of untreated mice (n = 20) and 14% of lamivudine-treated mice (n = 22) had detectable HBV DNA levels [limit of detection (LOD) < 5 x 10^3 copies/ml; $p < 0.0001$]. Mean HBV DNA levels were reduced by 97% on day 16 in lamivudine-treated mice (from 2.9 x 10^5 to 9.4 x 10^3 copies/ml; $p < 0.0001$), but increased substantially within 5 days of the cessation of treatment (to 7.3 x 10^4 copies/ml; 64% of mice had detectable HBV DNA).[30]

2.1.3 Resistance

Lamivudine-resistant HBV variants have been isolated from patients with chronic hepatitis B during treatment with lamivudine.[31-80] A point mutation in a highly conserved region of the HBV genome that codes for the catalytic site of the DNA polymerase has consistently been identified in lamivudine-resistant clinical isolates. The wild-type amino acid sequence in this region, Tyr-Met-Asp-Asp (YMDD), is also found in the DNA polymerase of other hepadnaviruses and in HIV reverse transcriptase.[35] Substitution of methionine by valine (M552V) or isoleucine (M552I) in this motif has been documented in patients with resistance to lamivudine. Identical mutations in the YMDD motif of HIV reverse transcriptase confer resistance to lamivudine. A second mutation (L528M), which results in methionine replacing leucine 24 amino acids upstream of the mutation in the YMDD motif, has been identified in association with M552V and M552I.[1] L528M confers cross-resistance to famciclovir;[49,59,81] however, lamivudine-resistant HBV does not appear to be cross-resistant to adefovir.[83-86]

The EC_{50} of lamivudine increased 45-fold (from 0.01 to 0.45 μmol/L) in primary human hepatocytes inoculated with serum samples obtained before and after treatment in a patient with acquired lamivudine resistance.[36] Genotypic analysis of HBV isolated from the patient revealed the presence of M552V in the latter samples.[36]

HBV constructs containing YMDD variants with and without L528M were resistant to lamivudine when transfected into HepG2 cells. The EC_{50} of lamivudine was 153-[42] 550-[87] and 3010-fold greater[87] for HBV containing M552V, M552I and L528M plus M552V, respectively, than for that containing wild-type HBV. In 1 study, the EC_{50} of lamivudine exceeded the cytotoxic concentration (>10 000-fold increase in EC_{50}) in cells containing

1 In some studies the methionine residue in the YMDD motif is referred to as position 550 and the upstream leucine residue is referred to as position 526.[36,43,52,53,55,81,82]

HBV constructs with M552I, or M552V or M552I in conjunction with L528M (i.e. the EC_{50} could not be determined).[42]

The inhibition constant for lamivudine triphosphate increased 8- to 25-fold when M552I, M552V or M552V and L528M were introduced into HBV polymerase.[84]

YMDD variant HBV was replication deficient *in vitro*. Viral constructs with M552V,[88] M552I[88,89] or L528M plus M552V[89] had lower replication rates than wild type virus in human hepatocellular carcinoma cell lines (HepG2 and HUH-7).

In patients with chronic hepatitis B, YMDD variant HBV predominated only when selected for by lamivudine and upon withdrawal of lamivudine, wild-type virus was restored. In 5 patients who had received lamivudine 100 mg/day for ≥12 months, HBV variants (M552V or M552I) were detected by polymerase chain reaction (PCR) in sera collected 1 to 4 months prior to a marked increase in HBV DNA levels.[43] After lamivudine resistance became apparent and the drug was withdrawn, the previously dominant variant HBV population was eclipsed by wild-type virus and HBV DNA levels returned to pretreatment values.[43,46,51] In many patients in whom lamivudine therapy was continued in spite of the presence of resistant virus, HBV DNA levels remained below pretreatment values.[43,46,51]

These findings suggest that, in accord with the *in vitro* data cited above, YMDD variant HBV in patients with chronic hepatitis B is replication deficient compared with wild-type virus. Although marked increases in ALT levels have occurred after the development of resistance, ALT levels have generally been greater in patients who stop lamivudine than in those who continue taking the drug.[43,51] The authors of 1 report suggest continuing the drug in patients with YMDD variant HBV because HBV DNA levels and ALT levels tend to remain below pretreatment levels when therapy is continued.[51] Controlled studies with long durations of follow-up would be required to confirm the validity of this strategy.

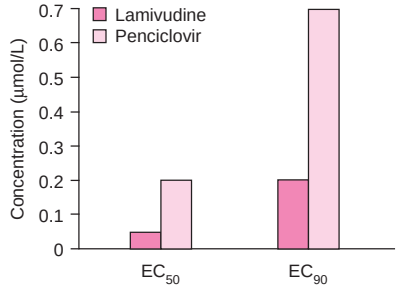

Fig. 4. Activity of lamivudine against hepatitis B virus (HBV) *in vitro*. Concentrations of lamivudine and penciclovir (the active metabolite of famciclovir) that reduced HBV virion DNA levels by 50 (EC_{50}) and 90% (EC_{90}) in the culture medium of an HBV-producing human hepatocellular carcinoma cell line (2.2.15).[21]

YMDD variant HBV was slow to become apparent and was detected 12 to 116 weeks after initiating therapy in patients with chronic hepatitis B.[31,34-38,40,41,43,44,46,47,52,57-66,68-72,74,75,77,90] After 9 and 12 months of therapy, respectively, 10 (4%) and 37 (14%) of 285 Chinese patients treated with lamivudine (25 or 100 mg/day) had acquired YMDD variant HBV genotypes.[45] In a pooled analysis of 4 large, controlled, multicentre trials in which 558 patients received lamivudine, 16 to 32% of patients treated with lamivudine 100 mg/day had acquired YMDD variant HBV after 52 weeks (the Chinese study referred to above was included in this analysis).[90] Exploratory analyses showed that, after 24 weeks' treatment, those patients who were HBeAg-positive, had ALT levels >1.3 times the upper limit of normal (ULN) and HBV DNA levels >20 pg/ml (by HBV DNA solution hybridisation assay) had a 99% chance of harbouring YMDD variant HBV.[90] High pretreatment viral loads appear to be a predisposing factor for the emergence of YMDD variant HBV.[58,65] The therapeutic response of patients carrying YMDD variant HBV is described in section 4.1.1.

HBV has a compact genome in which the open reading frame for HBsAg is overlapped entirely by that of the polymerase. Hence, mutations in the reading frame may result in amino acid substitutions in both polymerase and HBsAg. However, the portion of HBsAg that incorporates the sequence corresponding to the YMDD motif of polymerase is embedded in the lipid envelope and does

not contribute to the antigenicity of the protein.[42] Thus, substitution of isoleucine or valine for methionine in the YMDD motif did not alter the synthesis or binding properties of HBsAg.[88,89,91]

2.2 Cytotoxicity

Lamivudine does not interfere with human DNA synthesis and exhibits little cytotoxicity toward human cell lines (table I). The 3'-5' exonuclease activity of DNA polymerase γ was capable of excising lamivudine 5′-monophosphate incorporated during chain termination assays.[97] Moreover, at clinically relevant concentrations (0.01 to 0.03 μmol/L) lamivudine did not appreciably inhibit DNA synthesis in intact mitochondria.[17]

Delayed mitochondrial toxicity is thought to be the mechanism of several adverse effects associated with nucleoside analogues, including fialuridine-induced hepatotoxicity,[99-102] peripheral neuropathy induced by zalcitabine,[101,103,104] pancreatitis associated with didanosine,[101] zidovudine-induced myopathy[101,105] and haematotoxicity associated with 3'-fluoro-3'-deoxythymidine.[93] For this reason, the structure and function of hepatocellular mitochondria were investigated by serial liver biopsy and non-invasive 2-keto[l-^{14}C] isocaproic acid (KICA) breath testing in 15 patients receiving lamivudine 25 to 300 mg/day for chronic hepatitis B.[98] No evidence of mitochondrial toxicity was detected at any time during the 24-week study (table I).

2.3 Effects on Immune Function in Patients With Chronic Hepatitis B

An ineffective host cellular immune response contributes to the development of chronic hepatitis B infection.[106] Furthermore, high levels of HBV in patients with chronic hepatitis B may suppress

Table I. Results of human cytotoxicity studies with lamivudine

Cell growth and metabolism *in vitro*	The CC_{50} for lamivudine ranged from 150 to 3000 μmol/L and the therapeutic index[a] was >1000 (2.2.15 and HB 611 cells)[22,23]
	Lamivudine >20 μmol/L inhibited growth by 50% in 2.2.15, CEM and MT2 cells[25,92]
	Lamivudine 0.1 to 10 μmol/L did not affect cell density, lactic acid formation, mitochondrial morphology or mitochondrial DNA synthesis in HepG2 cells[93]
	Lamivudine <25 μmol/L did not inhibit cell growth, mitochondrial DNA synthesis or neurite regeneration in PC12 cells[94]
	Lamivudine 10 to 200 μmol/L did not interfere with deoxynucleotide metabolism in U937 cells,[95] and at 1 μmol/L the drug did not alter levels of deoxynucleotide triphosphates in CEM cells[16]
Mitochondrial toxicity *in vitro*	Lamivudine 5′-triphosphate inhibited partially purified DNA pol γ somewhat, (the 50% inhibitory concentration was 43.8 μmol/L in 1 study,[96] and the Ki was reported to be 0.01 μmol/L in a further study[17]), and lamivudine >50 μmol/L reduced mitochondrial DNA concentrations by 50% in CEM cells[25]
	In chain termination assays, the 3'-5' exonuclease activity of DNA pol γ excised incorporated lamivudine 5′-monophosphate[97]
	Lamivudine was not phosphorylated by mitochondrial deoxypyrimidine nucleoside kinase in cellular extracts,[92] or in intact mitochondria (2.2.15 cells)[94]
	Lamivudine 0.01 to 0.03 μmol/L did not inhibit DNA synthesis in intact mitochondria[17]
Mitochondrial structure and function in 15 patients with chronic hepatitis B receiving lamivudine 25 to 300 mg/day for 24 weeks[98]	Electron microscopy detected no morphological changes in mitochondria in liver biopsy specimens obtained from patients before or during treatment with lamivudine
	There was no difference in KICA decarboxylation[b] in patients before, during or after lamivudine treatment, and no difference between patients and volunteers
	The activity of mitochondrial DNA-encoded enzyme systems was similar in liver biopsy specimens obtained before and during treatment with lamivudine

a Therapeutic index = CC_{50}/EC_{50}.

b As determined by non-invasive breath testing.

DNA pol γ = human DNA polymerase γ (mitochondrial DNA polymerase); **CC_{50}** = concentration required to produce a 50% reduction in incorporation of tritiated deoxythymidine; **EC_{50}** = concentration required to reduce HBV DNA levels in the cell culture medium by 50%; **KICA** = 2-keto[1-^{14}C] isocaproic acid.

cytokine-mediated cellular immune responses.[107] Thus, therapies which suppress HBV levels may restore T cell responsiveness in patients with chronic hepatitis B.

Cellular immune responsiveness increased during treatment with lamivudine in patients with chronic hepatitis B. Statistically significant increases in proliferation of T cells [in response to stimulation with nucleocapsid antigens (HBeAg and HBcAg)] obtained from 12 HBV DNA-positive, HBeAg-positive patients with chronic hepatitis B occurred during treatment with lamivudine 100 mg/day ($p < 0.05$ vs pretreatment). The recovery in T cell responsiveness was temporally associated with suppression of HBV DNA levels in these patients.[108] In contrast, there was no difference in recombinant HBcAg-stimulated proliferation of PMBCs obtained from 9 patients with chronic hepatitis B before, during, or after treatment with lamivudine 100 mg/day plus interferon-α 30 MU/week.[109] However, in the latter study, the antiproliferative effects of interferon-α may have prevented restoration of T cell responsiveness despite suppression of viral replication by lamivudine.[108]

3. Pharmacokinetic Properties

A comprehensive review of the pharmacokinetics of lamivudine, which includes data in patients with chronic hepatitis B, was recently published.[19] This section provides a brief overview of these data, supplemented by information obtained from other patient groups and healthy volunteers.

Lamivudine is well absorbed after oral administration and is widely distributed in the body. Wide interindividual variation in absorption of lamivudine has been reported (reviewed by Johnson et al.[19]). For example, in HIV-positive patients receiving single oral doses of 100mg (n = 12), the mean absolute bioavailability was 86 to 88%; however, individual values ranged from 53 to 105%.[110] Food delays but does not alter the extent of absorption; hence, the drug can be administered without regard to meals.[111] Lamivudine is not extensively bound to plasma proteins (36%), distributes into total body fluid (volume of distribution 1.3 L/kg) and crosses the placenta (the drug is present in amniotic fluid), where concentrations appear to equilibrate between the maternal and foetal circulation.[19,112] The neonatal to maternal serum concentration ratio of lamivudine was 1.03 after administration of 300mg twice daily for a median of 13.7 days in HIV-positive women prior to parturition (n = 8).[19,112] Lamivudine is also excreted in breast milk.[112]

The pharmacokinetics of lamivudine in patients with chronic hepatitis B are generally similar to those in HIV-positive patients.[19] Serum concentrations show a linear dose-dependent profile.[19] Steady state pharmacokinetic parameters in 6 patients with chronic hepatitis B receiving lamivudine 100 mg/day are presented in table II.

In children aged 2 to 12 years with chronic hepatitis B the pharmacokinetics of lamivudine were generally similar to those in HIV-positive paediatric patients.[19,113] A dosage of 3 mg/kg once daily in children aged 2 to 12 years resulted in similar steady state parameters [area under the plasma concentration versus time curve (AUC) $\geq$4 mg/L · h; maximum plasma concentration (C_{max}) $\approx$1.5 mg/L and minimum plasma concentration (C_{min}) $\geq$0.02 mg/L) to those in adults with hepatitis B receiving 100 mg/day.[113] Clearance of lamivudine was higher in children than in adults, but declined with age such that, by the age of 12 years, it was generally equivalent to clearance in adults (quantitative data were not presented in this abstract).[113]

Renal excretion is the major route of elimination for lamivudine.[19] Renal clearance (Cl_r) of lamivudine exceeds the glomerular filtration rate;

Table II. Steady state pharmacokinetic properties of oral lamivudine 100 mg/day in 6 adult patients with chronic hepatitis B[19]

Parameter	Mean (range)
C_{max} (mg/L)	1.1 (0.8 to 1.6)
t_{max} (hours)	1 (0.5 to 4)
AUC_{24} (mg/L • h)	4.72 (3.4 to 6.5)
$t_{½\beta}$ (hours)	6.2 (4.0 to 9.5)

AUC_{24} = area under the plasma concentration versus time curve from 0 to 24 hours after a dose; **C_{max}** = maximum plasma concentration; **t_{max}** = time to C_{max}; **$t_{½\beta}$** = terminal elimination half-life.

hence active tubular secretion plays an important role in lamivudine excretion.[114] Less than 5% of a dose is eliminated as an inactive trans-sulphoxide metabolite.

Moderate or severe renal dysfunction significantly alters elimination of lamivudine. Lamivudine clearance declined in proportion to the creatinine clearance (Cl_{cr}) in healthy volunteers and volunteers with moderate or severe renal dysfunction.[115] As a result, the dosage of lamivudine should be modified in patients with moderate or severe renal dysfunction [i.e. in those with Cl_{cr} < 3 L/hr (<50 ml/min); see section 6].[115,116] Haemodialysis had a modest effect on lamivudine pharmacokinetics in 6 volunteers with severe renal dysfunction receiving a single 100mg dose; oral clearance (Cl/F) was increased by 27% and the mean AUC was decreased by 24%.[115] The magnitude of these changes do not warrant further modification of the dosage beyond that mandated by the Cl_{cr} in patients undergoing haemodialysis.[116]

The AUC, C_{max}, time to achieve C_{max} (t_{max}), Cl/F and Cl_r of a single 300mg oral dose of lamivudine were not statistically different in 16 patients with moderate or severe hepatic impairment (according to the results of a ^{14}C-aminopyrine breath test and by Child-Pugh criteria) due to cirrhosis (unrelated to hepatitis B) and healthy controls (n = 8).[117] Hence, dosage modifications are not warranted in patients with decompensated liver disease.[117]

Mean AUC_∞ and Cl/F in 6 healthy elderly (aged ≥65 years) Japanese men were 1.4 and 0.71 times those of 6 healthy young men (mean age 20.8 years; $p < 0.05$ for elderly *vs* young men), respectively, after a single 100mg oral dose of lamivudine.[118] Nonetheless, C_{max} and $t_{½\beta}$ of lamivudine were similar in the 2 groups. Cl_r of lamivudine in the elderly men was 0.67 times that in young men ($p < 0.0l$) and AUC and Cl_r were significantly correlated with creatinine clearance [Cl_{cr}; mean = 4.8 L/hr (79.7 ml/min) in elderly men and 6.6 L/hr (110.8 ml/min) in young men].[118] The authors of the study concluded that, in the absence of renal dysfunction, dosage adjustments were not required in elderly patients.[118]

3.1 Pharmacokinetic Drug-Drug Interactions

Lamivudine is not extensively bound to plasma proteins, has a low metabolic clearance and has no effect on drug metabolism *in vitro*; hence, lamivudine has little potential for drug-drug interactions with drugs that are extensively metabolised and/or highly plasma protein bound.[19]

The pharmacokinetics of lamivudine 100 mg/day were not altered by coadministration of interferon-α 30 MU/week for 4 weeks in 14 patients with chronic hepatitis B.[119] In patients with HIV infection, there is no drug-drug interaction between lamivudine and zidovudine.[19]

There is a pharmacokinetic drug-drug interaction between lamivudine and cotrimoxazole (trimethoprim-sulfamethoxazole).[120] In patients with asymptomatic HIV infection (n = 14) who received a single 300mg dose of lamivudine, the AUC increased by 44% and Cl_r decreased by 35% after receiving cotrimoxazole 800/160 mg/day for 4 days.[121] The pharmacokinetics of cotrimoxazole were unaffected by lamivudine in this study. The putative mechanism for the interaction is competitive blockade of active tubular secretion of lamivudine by the trimethoprim component of cotrimoxazole.[120] Although cotrimoxazole is frequently used as prophylaxis against *Pneumocystis carinii* infection in orthotopic liver transplant recipients and in HIV-positive patients, 2 populations likely to receive lamivudine for chronic hepatitis B, this interaction is unlikely to be clinically significant. However, it remains to be determined whether the interaction between lamivudine and cotrimoxazole is clinically relevant in patients receiving much higher dosages of cotrimoxazole as treatment for *P. carinii* pneumonia or in patients with severe renal dysfunction.

4. Therapeutic Potential in Chronic Hepatitis B

Lamivudine has been studied in a wide variety of patients with HBV. Randomised, placebo-controlled trials have been conducted in immunocompetent patients with chronic hepatitis B and

compensated liver disease,[45,122-125] including HBeAg-negative, HBV DNA-positive patients presumed to be infected with HBV pre-core variants.[126] The drug has also been studied in HBV DNA-positive liver transplant candidates with end-stage liver disease.[32,76,127-136] The effect of lamivudine in HIV-positive patients co-infected with HBV has been described.[79,137-146] Lamivudine has been used in liver transplant,[32,33,52,57,76,77,147-169] renal transplant[50,170-176] and allogeneic[177] and autologous[178] bone marrow transplant recipients and in patients undergoing intensive chemotherapy for cancer[176,179-181] with recurrent or *de novo* chronic hepatitis B, including patients with fibrosing cholestatic hepatitis[172-174] and those unresponsive to famciclovir.[52,59,148,151,156,161,162,182,183] Lamivudine plus hepatitis B immune globulin (HBIg) have been used to prevent HBV infection in nonimmune recipients of hepatic allografts obtained from anti-HBc-positive donors.[184] The use of the drug in patients with chronic hepatitis B and decompensated liver disease has been reported.[185] Lamivudine has also been used in patients with acute hepatitis B infection,[186] including patients with fulminant hepatitis[187-189] or cholestasis.[190] Preliminary results of a dose finding study in paediatric patients with chronic hepatitis B are also available.[113]

The most meaningful end-points in intervention studies in chronic hepatitis B would be measures of morbidity, such as progression of cirrhosis, the requirement for transplantation or the incidence of hepatocellular carcinoma, and mortality, but long term studies in large numbers of patients are required to evaluate such outcomes.

In the absence of such studies, a variety of markers were used to evaluate the efficacy of lamivudine in patients with chronic hepatitis B. Histological improvement in liver biopsy specimens was the primary[45,122,125,191] or a secondary[126] end-point in several studies. Other outcome variables included quantitative measurements of HBV DNA levels, HBeAg seroconversion rates and normalisation of ALT levels during treatment with lamivudine.

The Knodell histological activity index was used to grade liver biopsy specimens.[45,78,122,126,191,192] The Knodell score is the sum of scores assigned for periportal bridging necrosis (0 to 10), intralobular degeneration and focal necrosis (0 to 4), portal inflammation (0 to 4) and fibrosis (0 to 4).[193] Thus, the assigned score ranges from 0 (no pathology) to 22 (severe disease). The first 3 components are measures of necroinflammatory activity and the fourth component, fibrosis, represents the healing of necroinflammation.[194] Hence, the sum of the first 3 components (referred to as the Knodell necroinflammatory score) was used as an indication of necroinflammatory activity in most studies.[45,78,122,125,126,191] A histological response was consistently defined as a decrease of 2 or more points in the Knodell necroinflammatory score since in untreated patients the index often increases by 2 or more points per year and spontaneous decreases of 2 or points are rare.[45] Immunohistochemical staining for markers of HBV infection (HBcAg, HBsAg) and qualitative determination of HBV DNA in liver biopsy specimens were done in 1 study.[45]

Quantitative HBV DNA determinations were the most commonly used measure of virus replication. The HBV DNA solution hybridisation assay was used in many studies to quantify HBV DNA concentrations in serum, although this assay is less sensitive and precise than other commercially available quantitative assays including the branched DNA probe assay.[7,195,196] Qualitative and quantitative PCR assays, which are generally more sensitive than HBV DNA solution hybridisation or branched DNA probe quantitative assays,[197] were used in some studies.

4.1 Studies in Immunocompetent Adults With Chronic Hepatitis B and Compensated Liver Disease

In preliminary dose finding studies of 4 to 24 weeks' duration, lamivudine 2.5 to 600 mg/day was evaluated in immunocompetent adults with chronic hepatitis B and compensated liver disease.[198-203] In general, all dosages of lamivudine

suppressed HBV replication to some extent during treatment, and after lamivudine was discontinued serum HBV DNA levels generally returned to baseline.[198-202] Dosages ≥25 mg/day were capable of reducing HBV DNA levels below the limit of detection (HBV DNA solution hybridisation assay; LOD ≤1.5 pg/ml) within 2 to 4 weeks.[199,201] In 1 study, HBV DNA levels were suppressed below the LOD ($\leq 10^3$ genome equivalents/ml) of a sensitive quantitative PCR assay in 46% of patients treated with lamivudine 25 to 300 mg/day for 24 weeks.[204] Dosages of 100 and 300 mg/day provided significantly greater ($p < 0.05$) HBV DNA suppression than 25 mg/day in this study.[204] Six months' treatment with lamivudine 25 to 300 mg/day also reduced necroinflammatory activity in liver biopsy specimens obtained from patients with chronic hepatitis B.[192] The results of dose ranging studies with lamivudine in patients with chronic hepatitis B suggest that daily dosages ≥100 mg/day are optimal;[198,199,201,202,205] a dosage of 100 mg/day was generally used in subsequent clinical trials.

Patients enrolled in clinical trials with lamivudine were HBV DNA-positive,[45,78,119,122,126,191,206] had been HBsAg-positive[45,119,126] and either HBeAg-positive[45,119] or HBeAg-negative[126] for ≥6 months and had compensated liver disease. Several studies required HBV DNA levels to exceed a prescribed threshold (i.e. ≥2.5;[126] ≥5;[45] or ≥10 pg/ml[119]). ALT levels were required to be <10 times the ULN prior to inclusion in 2 studies.[45,126]

In the 1 placebo-controlled study in HBeAg-negative patients the presence of precore mutants was not confirmed by DNA sequencing.[126] However, more than 98% of HBeAg-negative individuals with chronic hepatitis B in the Mediterranean region, where most of the study sites were located, harbour precore mutant HBV.[207]

In 2 studies, only patients who had failed to seroconvert from HBeAg-positive to anti-HBe with interferon-α were eligible for enrolment.[119,125] In other studies, patients may have received a previous, unsuccessful course of interferon-α therapy, but were excluded if they had recently received corticosteroids, or other immunomodulatory or antiviral therapy.[45] Some studies excluded patients co-infected with HIV, hepatitis C or D or those with decompensated liver disease.[45,119,126]

Patients had biopsy-proven chronic hepatitis B in 1 study and, based on the results of the pretreatment liver biopsy, were stratified as having mild or moderate to severe hepatitis.[45]

The effects of lamivudine in immunocompetent patients with chronic hepatitis B and compensated liver disease have also been described in case series and case reports,[54,73,130,208-221] the results of which are not included here.

4.1.1 Lamivudine Versus Placebo

The effect of 1 year's treatment with lamivudine in HBeAg-positive adults with chronic hepatitis B and compensated liver disease was evaluated in 2 randomised, double-blind, placebo-controlled studies.[45,122] In 1 study, 357 Chinese patients aged 16 to 70 years received lamivudine 25 or 100 mg/day or placebo for 52 weeks.[45] In the second study, which was published as an abstract, 137 Western patients received lamivudine 100 mg/day or placebo for 52 weeks after which treatment was discontinued and patients were monitored for 16 weeks.[122]

Lamivudine produced profound suppression (i.e. below the LOD) in HBV DNA levels in both Chinese and Western patients (table III). Significantly more Chinese patients treated with lamivudine 100 mg/day had undetectable HBV DNA levels (LOD ≤1.6 pg/ml) at some point during the 52-week study than either lamivudine 25 mg/day or placebo recipients ($p < 0.001$ for both comparisons), although it should be noted that baseline HBV DNA levels were significantly ($p = 0.04$) higher in placebo recipients than in patients treated with lamivudine 25 mg/day.[45] In Western patients HBV DNA levels increased after withdrawal of lamivudine 100 mg/day.[122]

In concert with suppression of HBV replication, lamivudine produced clinically significant histological improvements in Chinese and Western patients with chronic hepatitis B (table III).[45,122] After 52 weeks of treatment, 56% of Chinese and

Table III. Effect of oral lamivudine (LAM) in adults with chronic hepatitis B in multicentre, randomised, double-blind, placebo-controlled trials

Study design [duration of treatment (wk)]	Treatment (mg/day) [no. of patients]	Baseline characteristics		Outcome (end of treatment)				
		serum HBV DNA-positive (% of patients)	serum HBV DNA (pg/ml)	serum HBV DNA below LOD (% of patients)	change in serum HBV DNA (%)	histological improvement (% of patients)[a]	worsening fibrosis in liver biopsy (% of patients)	overall efficacy
HBeAg-positive, HBV DNA-positive patients								
Dienstag et al.[122] [52] abstract	LAM 100 (66)		199[bc]	44***[c]		52***	5**	LAM > PL
	PL (71)		107[bc]	16[c]		23	20	
Lai et al.[45] [52]	LAM 25 (142)	95[d]	47*[bd]	73[de]	↓93[f]	49***	6[g]	LAM > PL
	LAM 100 (143)	98[d]	63[bd]	96[de]***[†]	↓98[f]***[†]	56***	3[g]**	
	PL (72)	97[d]	71[bd]	23[de]	↓54[f]	25	15[g]	
Tanikawa et al.[123] [16] abstract	LAM 100 (66)		501[bh]		↓99.7[b]			LAM > PL
	PL (71)		316[bh]		↓50[b]			
Yao et al.[124] [12] abstract	LAM 100 (322)	100		92[e]***				LAM > PL
	PL (107)	100		14[e]				
HBeAg-negative, HBV DNA-positive patients								
Tassopoulos et al.[126] [26]	LAM 100 (60)	92[h]	255[fh]	91[hi]		42[j]	2	LAM > PL
	PL (64)	86[h]	95.5[fh]	26[hi]		NA	NA	

a Defined as a decrease of ≥2 points in Knodell necroinflammatory score *vs* baseline. The Knodell necroinflammatory score comprises the sum of scores for periportal bridging necrosis (0 to 10), intralobular degeneration and focal necrosis (0 to 4), and portal inflammation (0 to 4) in liver biopsies. The median baseline score was 6 among patients enrolled in the study by Lai et al.[45] and was 5 and 7 in patients randomised to lamivudine or placebo, respectively, in the trial by Tassopoulos et al.[126]

b Mean.

c HBV DNA assay not described.

d HBV DNA solution hybridisation assay LOD ≤1.6 pg/ml.[45,124]

e On at least 1 occasion during the study.

f Median.

g Derived from graphs.

h Branched DNA probe assay LOD ≤2.5 pg/ml.

i At 24 weeks.

j By intention to treat analysis at 52 weeks.

HBeAg = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV DNA** = hepatitis B virus DNA; **LOD** = limit of detection; **NA** = not available; **PL** = placebo; ↓ = decrease; > = indicates that lamivudine was significantly more effective than placebo; *p = 0.04; **p ≤ 0.01; ***p ≤ 0.001 *vs* placebo; [†]p < 0.001 *vs* LAM 25mg.

52% of Western patients treated with lamivudine 100 mg/day, but ≤25% of placebo recipients, had a clinically significant reduction in the Knodell necroinflammatory score (defined as a ≥2 point reduction) compared with baseline ($p \leq 0.001$ for lamivudine 100 mg/day *vs* placebo).[45,122] A greater proportion of Chinese patients with moderate to severe hepatitis at baseline experienced histological improvement than those with mild hepatitis, although a statistical analysis of this trend was not presented (fig. 5).[45]

Liver disease was more likely to progress in placebo than lamivudine recipients. Among Chinese patients, 26% of placebo and ≤8% of lamivudine 25 or 100 mg/day recipients had increased necroinflammatory activity after 52 weeks of treatment.[45] Moreover, ≥15% of placebo recipients enrolled in these 2 trials had worsening fibrosis after 52 weeks of treatment compared with ≤5% of lamivudine 100 mg/day recipients ($p \leq 0.01$; table III).[45,122]

In contrast to the consistent reduction in serum HBV DNA levels and general improvements in liver histology in response to lamivudine treatment, there was no change in hepatocyte HBV DNA or HBcAg levels detected by immunohisto-

chemical staining in biopsy specimens collected at baseline and after 52 weeks of treatment with lamivudine 25 or 100 mg/day or placebo.[45]

Lamivudine-treated patients were more likely to experience HBeAg seroconversion than placebo recipients. Significantly more Chinese (16 *vs* 4%, $p = 0.02$)[45] and Western patients (17 *vs* 6%, $p < 0.04$;[122] fig. 6) treated with lamivudine 100 mg/day than placebo converted from HBeAg-positive to anti-HBe during 52 weeks of treatment. Among Chinese patients, those converting from HBeAg to anti-HBe had lower HBV DNA levels, higher ALT levels and higher median Knodell necroinflammatory scores at baseline than nonresponders.[45] In the Western study, suppression of HBeAg without seroconversion to anti-HBe occurred in approximately 3-fold more patients treated with lamivudine 100 mg/day than placebo (32 *vs* 11%; fig. 6); 80% of these patients remained HBeAg-negative after 16 weeks of follow-up.[122] Seroconversion from HBsAg-positive to anti-HBs was not reported in any patient in either study.[45,122]

Lamivudine generally reduced ALT levels in these trials.[45,122] Among Chinese patients with elevated ALT levels at baseline [median baseline ALT was 1.5 times the upper limit of normal (ULN), and ranged up to 15-times the ULN; 243 of 357 patients had abnormal values] ALT levels normalised in 72 (68 of 95) and 65% (65 of 98), respectively, of those treated with lamivudine 100 and 25 mg/day, but in only 24% (12 of 50) of placebo recipients after 52 weeks ($p < 0.001$ for each dose *vs* placebo; fig. 7).[45] Abnormal elevations in aminotransferase levels were rare in Chinese patients during treatment with lamivudine (1.1%; 3 of 285 patients) and were less frequent than in patients receiving placebo (4.1%; 3 of 73 patients).[45]

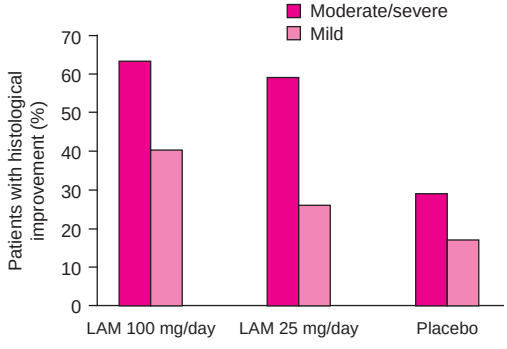

Fig. 5. Histological improvement in patients treated with lamivudine (LAM). Histological improvement in liver biopsies after 52 weeks of lamivudine 25 (n = 142) or 100 (n = 143) mg/day or placebo (n = 72) in Chinese patients with mild or moderate/severe necroinflammatory activity in baseline.[45] Histological improvement was defined as a reduction of ≥2 points in the Knodell necroinflammatory score.

In the Western study, ALT levels generally improved in patients treated with lamivudine 100 mg/day; however, in some patients, substantial increases in ALT levels occurred during treatment and follow-up. In patients in whom ALT levels were elevated at baseline, ALT levels normalised in significantly more lamivudine 100 mg/day than placebo recipients after 52 weeks' treatment (41 *vs* 7%; $p < 0.001$).[122] Grade 3 elevations in ALT (3.1- to 10-fold increases over baseline) occurred in <15% of patients in each group during treatment, and in 22 and 6% of lamivudine and placebo-treated patients, respectively, during 16 weeks of follow-up.[122] Grade 4 elevations in ALT (>10-fold increases over baseline) were documented in <5% of patients during follow-up, but were infrequently associated with bilirubin elevations (one patient in each group).[122]

At the end of the 52-week study in Chinese patients,[45] lamivudine 100 mg/day recipients were randomly allocated to a further 52 weeks of double-blind treatment with lamivudine 100 mg/day (n = 93) or placebo (n = 41).[222] HBV DNA levels remained suppressed below the LOD (≤1.6 pg/ml) for a further 52 weeks in 47 of 90 (52%) patients who continued lamivudine, but in only 2 of 41 (5%) patients assigned to placebo ($p < 0.001$ *vs* lamivudine 100 mg/day).[222] Moreover, the proportion of patients who seroconverted from HBeAg-positive to anti-HBe, among those treated continuously with lamivudine 100 mg/day, increased from 17% (16 of 93) after 1 year to 27% (25 of 93) after the second year. After 2 years of treatment with lamivudine 100 mg/day, ALT levels had normalised in 50% of patients. Data pertaining

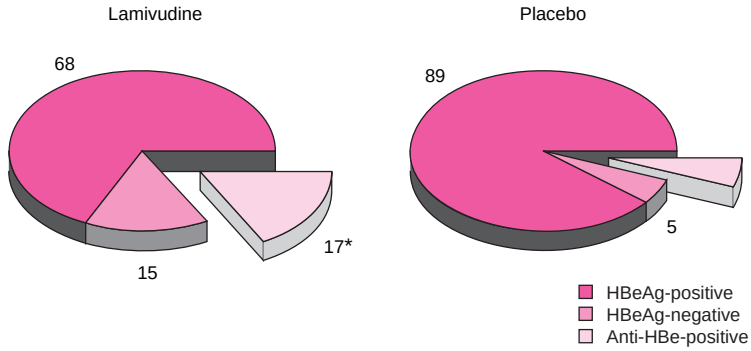

Fig. 6. Seroconversion during treatment with lamivudine. Percentage of patients who lost HBeAg and seroconverted to anti-HBe after 52 weeks of treatment with lamivudine 100 mg/day (n = 66) or placebo (n = 71) in a multicentre, randomised, double-blind US study.[122] Seroconversion was defined as the absence of HBeAg and HBV DNA, and the presence of anti-HBe in serum. All patients were HBeAg-positive prior to treatment. *p < 0.04 *vs* placebo. **Anti-HBe** = antibodies to HBeAg; **HBeAg** = hepatitis B e antigen; **HBV DNA** = hepatitis B virus DNA.

to placebo-treated patients were not provided in the abstract.[222]

In addition to continued suppression of HBV DNA replication and increased frequencies of HBeAg seroconversion and ALT normalisation, histological improvement continued throughout the second year of treatment with lamivudine in Chinese patients. Of 19 patients enrolled at 1 study site and treated with lamivudine 25 or 100 mg/day for 2 years, 89% had an improvement of ≥2 points in the Knodell necroinflammatory score. The median necroinflammatory score decreased from 7 at baseline to 4 and 1, respectively, after 1 and 2 years of continuous treatment with lamivudine 100 mg/day; there was no change in the median score for fibrosis (comparative data were not provided in the abstract).[223] Consistent with the finding after 52 weeks of treatment (see section 2.1.2), efficacy responses were apparently not affected by the presence of YMDD variants (5 patients had YMDD variant HBV).[45]

Data are now available from a further 52-week randomised extension of the Chinese study (i.e. some patients have received 3 years of treatment).[224] Among 58 Chinese patients who received lamivudine 100 mg/day continuously for 3 years, 44% had HBV DNA levels below the LOD (≤1.6 pg/ml) and 33% had seroconverted to anti-HBe.[224] After 3 years of continuous treatment with lamivudine 100 mg/day, 49% (27/55) of patients had acquired YMDD variant HBV.[224] In patients harbouring YMDD variants for ≥2 years who had continued to receive lamivudine 100 mg/day, median HBV DNA levels (5.9 *vs* 77.2 pg/ml at baseline) and median ALT levels (1.5 times ULN *vs* 2 times ULN at baseline) were lower than baseline values; comparative data from placebo-treated patients were not presented in the abstract.[224]

YMDD variant HBV is acquired by a considerable proportion of lamivudine recipients during

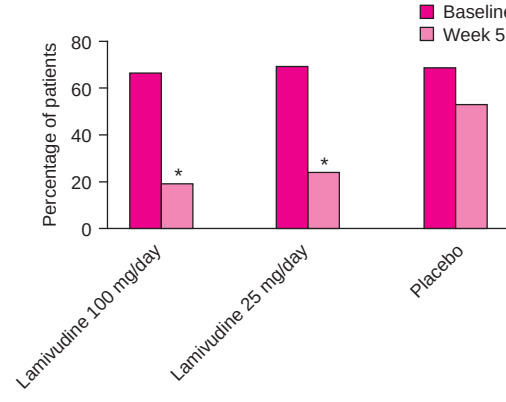

Fig. 7. Improvement in ALT levels during treatment with lamivudine in Chinese patients. Percentage of patients with elevated ALT levels at baseline and after 52 weeks of treatment with lamivudine 100 (n = 143) or 25 (n = 142) mg/day or placebo (n = 72) in a multicentre, randomised, double-blind study.[45] *p < 0.001 vs placebo.

treatment. 16 to 32% of patients enrolled in 4 large randomised, controlled, multicentre trials acquired YMDD variants after 52 weeks of treatment with lamivudine.[90] The median HBV DNA level was 80% lower than baseline in these patients and sustained ALT normalisation and histological responses were significantly more common in these patients than in those receiving placebo (the significance level was not provided in the abstract).[90] These findings suggest that, although lamivudine-resistant HBV emerges in some patients during long term lamivudine therapy, the status of these patients is generally improved over baseline when lamivudine therapy is continued. Nonetheless, comparative studies, in which patients with YMDD variants are allocated to further treatment with lamivudine or no treatment, are required to determine the optimal management strategy for patients with YMDD variant HBV. Until such studies are done, the management of such patients must be decided on an individual basis.

Lamivudine 100 mg/day suppressed HBV DNA levels below the LOD (≤1.6 pg/ml; $p < 0.001$ *vs* placebo; table III) and led to normalisation of ALT levels in a significantly greater proportion of patients than placebo in a 12-week, placebo-controlled trial conducted in Chinese patients (ALT levels normalised in 60% and 27% of lamivudine or placebo recipients respectively; $p < 0.01$).[124]

Lamivudine 100 mg/day reduced HBV DNA, HBeAg and ALT levels in Japanese patients with chronic hepatitis B. Mean HBV DNA levels were considerably lower in lamivudine- than placebo-treated patients (table III).[123] Mean ALT levels declined significantly from 143 IU/L at baseline to 41.5 IU/L at end-point in lamivudine 100 mg/day recipients. In placebo recipients mean ALT levels remained elevated during the study (142.6 IU/L at baseline and 127.6 IU/L after 16 weeks) and 3 placebo recipients were hospitalised for serious ALT elevations (range 438 to 1016 U/L).[123] HBV DNA and ALT levels returned to baseline during 8 weeks of follow-up.

Clinically significant improvements in liver histology were obtained in Japanese patients treated with lamivudine 100 mg/day for 52 weeks in a noncomparative study.[78] Among the 20 patients enrolled in the study (11 of whom were HBeAg-negative), a reduction of ≥2 points in Knodell necroinflammatory score between baseline and end-point was obtained in 19 and an improvement in fibrosis was noted in 7 (median necroinflammatory scores at baseline and end-point were 9 and 6, respectively; $p < 0.001$). YMDD variant HBV was detected in 1 patient during the study and in 5 further patients during treatment which extended beyond 52 weeks.[78]

A pooled analysis of data from 3 clinical trials provides evidence that treatment with lamivudine reduces the rate of progression to cirrhosis in patients with chronic hepatitis B. Of 578 patients enrolled in these trials 9% of those assigned to placebo and 5% of those assigned to lamivudine (dosage not specified) had cirrhosis at baseline (defined as a score of 4 on the fibrosis component of the Knodell histologic activity index).[225] The frequency of progression to cirrhosis after 1 year of treatment was 1.8 (4 of 219 patients), 7.1 (7 of 99 patients) and 9.5% (4 of 42 patients), in those treated with lamivudine 100 mg/day, placebo and interferon-α, respectively.[225]

Preliminary data suggest that anti-HBe seroconversion is durable after lamivudine is discontinued in patients with chronic hepatitis B. 31 of 34 patients who seroconverted during treatment with lamivudine (dosage not specified) in phase II and III clinical trials were anti-HBe-positive after a median follow-up of 6 months (range 0 to 12 months).[226] Comparative data were not provided in this abstract.[226] This suggests that withdrawal of lamivudine may be feasible in patients who experience HBeAg seroconversion. Large prospective studies with long durations of follow-up are required to confirm this suggestion.

In HBeAg-Negative, HBV DNA-Positive Patients with Chronic Hepatitis B

Patients with chronic hepatitis B who carry precore mutant strains of HBV generally do not respond as well to interferon-α as do HBeAg-positive patients. Although some patients infected,

or presumed to be infected, with precore mutants initially respond to interferon-α (i.e. become HBV DNA-negative), sustained responses are rare.[227,228] Thus, effective alternative antiviral therapies for chronic hepatitis B would be especially useful in such patients. The effect of lamivudine in HBeAg-negative, HBV DNA-positive patients with compensated liver disease presumed to be infected with precore mutant strains of HBV was studied in a multicentre, randomised, placebo-controlled trial.[126]

Similar to its effects in HBeAg-positive patients with chronic hepatitis B, lamivudine was generally effective in suppressing HBV replication and ameliorating liver disease in HBeAg-negative, HBV DNA-positive patients.[126] After 24 weeks' treatment, significantly more patients treated with lamivudine 100 mg/day than placebo had undetectable HBV DNA levels (LOD <2.5 pg/ml) and ALT levels within the normal range, the primary efficacy end-point in the study (fig. 8).[126] Lamivudine recipients with undetectable HBV DNA levels at week 24 continued lamivudine treatment for a total of 52 weeks; 65% of these patients (35 of 53) had a complete response after 1 year.[126]

When lamivudine was discontinued most patients experienced relapses. 24 weeks after discontinuing lamivudine therapy, 6 of 54 patients (11%) continued to have a complete response (30% of patients had undetectable HBV DNA levels and ALT levels were within normal limits in 17%).[229] This suggests that ongoing lamivudine therapy is required to provide ongoing suppression of HBV replication.

Partial responses, defined as undetectable HBV DNA levels without normalisation of ALT levels, occurred in 15 (28%) and 11 (20%) patients treated with lamivudine or placebo, respectively, for 24 weeks.[126] Although there were 5 (9%) nonresponders (HBV DNA ≥2.5 pg/ml) in the lamivudine group, serum HBV DNA levels after 24 weeks' treatment (range 3 to 38 pg/ml) were substantially lower than baseline levels. 74% of placebo recipients (40 of 54 patients) were nonresponders after 24 weeks' treatment.[126]

Hepatic necroinflammatory activity in these patients decreased significantly during treatment with lamivudine. Among those patients from whom evaluable liver biopsies were obtained at baseline and after 52 weeks' treatment with lamivudine, 60% (25 of 42) had a reduction of ≥2 points in the Knodell necroinflammatory score (biopsies were not obtained in placebo recipients); 5 patients

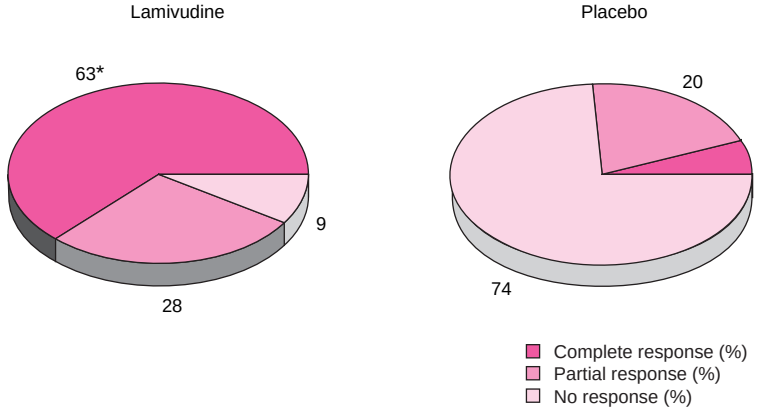

Fig. 8. Clinical responses to lamivudine in HBeAg-negative, HBV DNA-positive patients with chronic hepatitis B. Percentage of patients with complete responses (HBV DNA levels <2.5 pg/ml and normalisation of ALT levels) partial responses (HBV DNA levels <2.5 pg/ml without normalisation of ALT) or no response (HBV DNA levels ≥2.5 pg/ml) after 24 weeks' treatment with lamivudine 100 mg/day (n = 54) or placebo (54) in a multicentre, randomised, double-blind clinical trial.[126] **HBV DNA** = hepatitis B virus DNA; *p<0.001 *vs* placebo.

showed worsening of necroinflammatory activity (increase of ≥2 points).[126] The median Knodell necroinflammatory scores at baseline and week 52 were 5 and 2, respectively.[126] Moreover, fibrosis improved in 11% (5 of 44) and remained unchanged in 86% (38 of 44) of lamivudine recipients.[126] These results demonstrate that the effectiveness of lamivudine in HBeAg-negative patients with chronic hepatitis B is generally similar to that in HBeAg-positive patients.

4.1.2 Lamivudine Plus Interferon-α

In this section studies in which lamivudine was compared with interferon-α and/or combined with interferon-α will be reviewed.

The effect of lamivudine plus interferon-α in HBeAg-positive, HBV DNA-positive patients with compensated liver disease[119,125,191,206] and HBeAg-negative HBV DNA-positive patients with compensated liver disease[230] has been reported in several studies, most of which have been published as abstracts.[125,191,206,230] The combination was compared with monotherapy with lamivudine[125,191] or interferon-α.[119,191,206] One trial included a placebo group.[125]

Lamivudine combined with interferon-α therapy suppressed HBV DNA levels in HBeAg-positive patients with chronic hepatitis B (table IV). Only patients who had not responded to 1 or more previous courses of interferon-α therapy (≥13.5MU per week × ≥16 weeks) were included in 1 study;[119] HBV DNA levels remained detectable after 4 weeks of treatment with interferon-α in the 6 patients randomised to receive interferon-α plus placebo, but declined to below the LOD (≤3 pg/ml) when lamivudine 100 mg/day was added during the final 12 weeks of the study.[119]

Histological responses as measured by changes in the Knodell necroinflammatory score were measured in 2 studies in which patients in 1 treatment group received lamivudine plus interferon-α.[125,191] In both of these studies liver biopsies were obtained at baseline and after the completion of 52 weeks of treatment with lamivudine monotherapy[125,191] or placebo (fig. 9).[125] In patients randomised to lamivudine plus interferon-α[125,191] or interferon-α monotherapy,[191] liver biopsies were obtained at baseline and either 28 or 36 weeks, respectively, after the completion of therapy (i.e. 52 weeks after the initiation of therapy).

The pattern of histological responses differed between the 2 studies. In 1 trial, which enrolled only interferon-α-naive patients, there were no statistical differences among the 3 treatment groups in the proportion of patients with histological improvement (defined as an decrease of ≥2 in the Knodell necroinflammatory score; fig.9).[191] Unfortunately, a placebo group, which would have aided interpretation of these results, was not included in this study. Only patients who had not responded to a previous course of interferon-α were eligible for enrolment in the second trial and, in contrast to the results of the first study, histological improvements were significantly greater in patients treated with lamivudine 100 mg/day than in those treated with either lamivudine plus interferon-α ($p = 0.01$) or placebo ($p = 0.002$; fig. 9).[125] The clinical significance of these findings is unclear because biopsies were obtained at the end of treatment in patients receiving lamivudine monotherapy and after a lengthy period of follow-up in those treated with the combination or interferon-α monotherapy.

HBeAg seroconversion occurred in less than one-third of patients treated with lamivudine alone, interferon-α alone or the 2 drugs in combination (table IV). There were no statistical differences between treatment groups in the proportion of patients who experienced HBeAg seroconversion in any trial; however, the length of follow-up differed greatly between treatment groups, which hampers interpretation of the results.[119,125,191] In 1 trial, seroconversion rates 52 weeks after the initiation of therapy (and after 28 or 36 weeks of follow-up in patients treated with the combination or interferon-α monotherapy, respectively) ranged from 18 to 29%; 12 weeks later, seroconversion rates of 20, 22 and 25%, respectively, were documented in patients treated with lamivudine 100 mg/day for 52 weeks, interferon-α 30 MU/week alone for 16 weeks or combined lamivudine plus interferon-α

Table IV. Effect of oral lamivudine (LAM) plus subcutaneous interferon-α (IFN) in HBeAg-positive, HBsAg-positive patients with chronic hepatitis B in randomised trials

Study design [duration of treatment (wk)]	Treatment (mg/day)[a] [no. of patients]	Patients with elevated serum ALT levels at baseline (%)	Outcome (at end of treatment)			
			HBV DNA below LOD (% patients)	HBeAg seroconversion (% patients)	normalisation of serum ALT (% patients)	histological improvement (% patients)[b]
HBeAg-positive, HBV DNA-positive patients						
Heathcote et al.[191] mc, r, nb [52][c] abstract	LAM 100 x 52 weeks [82]	95		18	40†††	38
	IFN 30 MU/wk x 16 weeks [69]	96		19	17	36
	LAM 100 x 8 weeks, then LAM 100 plus IFN 30 MU/wk x 16 weeks [75]	95		29	25	28
Kim et al.[206] r, nb [24] abstract	LAM 150 plus IFN 13.5 MU/wk [12]	100	100[d]		75	
	IFN 13.5 MU/wk [14]	100	85[d]		64	
Mutimer et al.[119] mc, r, db, pc [16][e]	LAM 100 plus IFN 30 MU/wk [14]	79	100[f]	29	73	
	IFN 30 MU/wk plus PL X 4 weeks, then, LAM 100 plus IFN 30 MU/wk X 12 weeks [6]	100	100[f]	0	83	
Schiff et al.[125] mc, r, nb [52][ce] abstract	LAM 100 X 52 weeks [238][g]			18	44**††	52*†
	LAM 100 X 8 weeks, then LAM 100 plus IFN 30 MU/wk X 16 weeks			12	18	32
	PL X 52 weeks			13	15	25
HBeAg-negative, HBV DNA-positive patients						
Alexopoulou et al.[230] r, nb [26] abstract	LAM 150 plus IFN 13.5 MU/week [20]		95[h]			
	GAN 750 plus IFN 13.5 MU/week [20]		60[h]			
	No treatment [20]		NA			

a IFN was administered 3 times per week.

b Defined as a decrease of ≥2 points in Knodell necroinflammatory score (the sum of scores for periportal bridging necrosis, intralobular degeneration and focal necrosis, and portal inflammation in liver biopsies).

c Outcomes at week 52 are presented for this study. The median baseline Knodell necroinflammatory score in all patients was 4.

d HBV DNA assay not described.

e Patients had not responded to at least 1 previous course of IFN (≥ 13.5MU/week x ≥16 weeks[119]).

f Abbott HBV DNA solution hybridisation assay; LOD ≤3 pg/ml.

g Total number of patients enrolled in the study.

h Roche quantitative PCR assay; LOD ≤400 copies/ml.

db = double-blind; **GAN** = ganciclovir given orally; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV DNA** = hepatitis B virus DNA; **LOD** = limit of detection; **mc** = multicentre; **MU** = million units; **NA** = not available; **nb** = nonblind; **pc** = placebo-controlled; **PL** = placebo; **r** = randomised; *p = 0.002; **p<0.001 *vs* placebo; †p = 0.01; ††p = 0.005 for LAM *vs* LAM plus IFN; †††p = 0.007 for LAM *vs* IFN.

for 24 weeks.[191] Longer durations of follow-up will be required to determine the durability of HBeAg serconversion in these patients.

Normalisation of ALT occurred in patients receiving lamivudine monotherapy, interferon-α monotherapy and combined lamivudine plus interferon-α in comparative trials (table IV). Although ALT normalisation rates of 64 to 83% were obtained with combined lamivudine plus interferon-α or interferon-α monotherapy at the end of treatment in 2 trials, the durability of these responses was not reported in 1 trial[206] and in the other trial ALT levels returned to baseline during 16 weeks of follow-up.[119] Interpretation of the results in the other 2 trials is difficult because of the unusual study design.[125,191]

The effect of treatment for chronic hepatitis B on work productivity was assessed in 1 trial. Patients receiving lamivudine 100 mg/day plus interferon-α 30 MU/week for 24 weeks lost significantly more work-days (mean = 13.9) than patients receiving lamivudine 100 mg/day (mean = 7.1; $p < 0.001$ *vs* combination therapy) or placebo for 52 weeks (mean = 4.3; $p = 0.001$ *vs* combination ther-

apy).[231] There was no statistical difference in the number of work-days lost between lamivudine and placebo recipients.

In HBeAg-Negative, HBV DNA-Positive Patients with Chronic Hepatitis B

Lamivudine appears to be more effective than ganciclovir in suppressing HBV replication in patients with chronic hepatitis B. Preliminary results are available from 1 trial in which 60 patients with chronic hepatitis B were randomised to treatment with either lamivudine 150 mg/day plus interferon-α 13.5 MU/week, oral ganciclovir 750 mg/day plus interferon-α 13.5 MU/week or placebo.[230] After 26 weeks of treatment, a greater proportion of lamivudine plus interferon-α- than ganciclovir plus interferon-α-treated patients had HBV DNA levels below the limit of detection (LOD ≤400 copies/ml; table IV).[230] ALT levels normalised in all patients receiving active treatment. HBV DNA levels rebounded after withdrawal of antiviral therapy. Re-

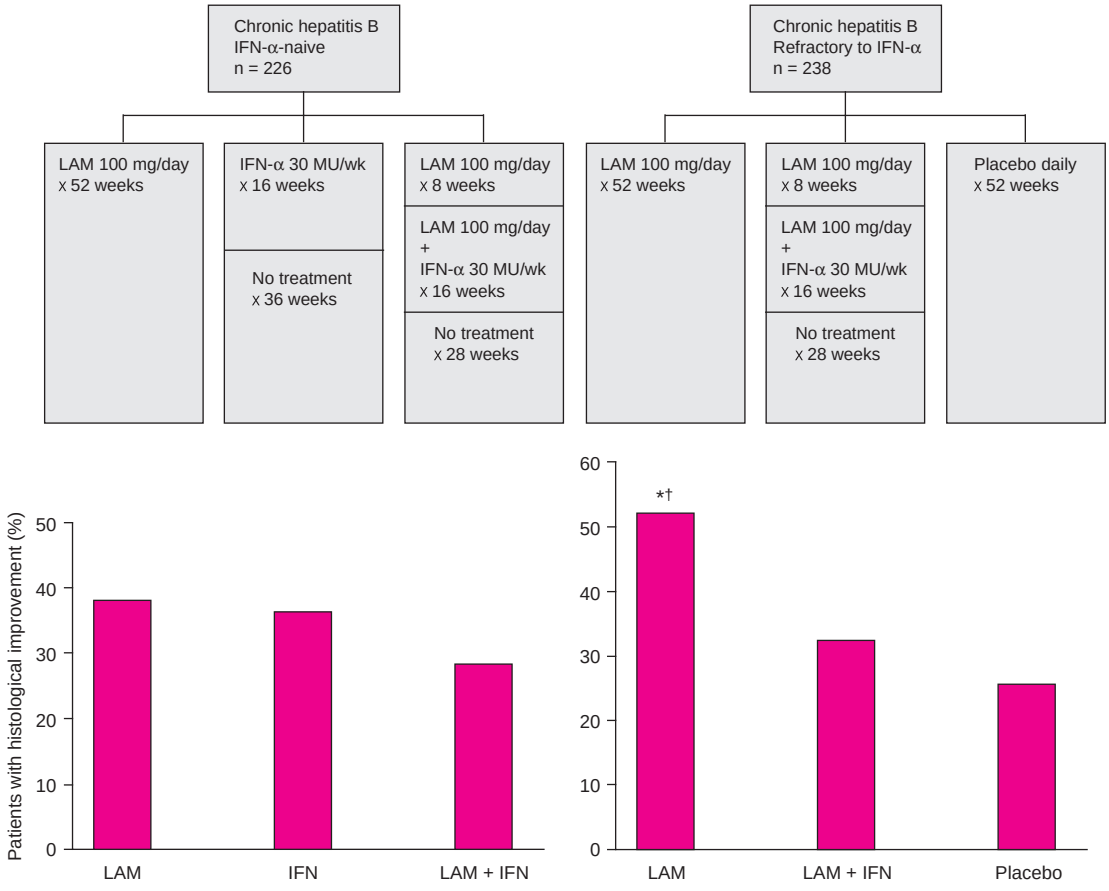

Fig. 9. Histological improvement in patients treated with lamivudine (LAM) alone, or in combination with interferon-α (IFN-α). Histological improvement in liver biopsies between baseline and at the end of treatment (i.e. week 52) in 2 randomised, multicentre studies which enrolled only IFN-α-naive,[191] or IFN-α-refractory patients.[125] In both studies, patients received lamivudine 100 mg/day alone for 52 weeks or lamivudine alone for 8 weeks then combined with IFN-α 30 MU/week for 16 weeks. A third group received IFN-α 30 MU/week alone in the study by Heathcote et al. (left);[191] or placebo for 52 weeks in the study by Schiff et al. (right).[125] Histological improvement was defined as a reduction of ≥2 points in the Knodell necroinflammatory score. *p = 0.002 for LAM vs placebo; †p = 0.01 for LAM vs LAM plus IFN-α.

sults in patients assigned to placebo treatment were not presented in the abstract.

4.1.3 Lamivudine Versus Famciclovir

Lamivudine monotherapy was more effective than famciclovir monotherapy in inhibiting HBV replication in patients with chronic hepatitis B. Preliminary data from a randomised, nonblind trial in which Chinese patients were treated with lamivudine 100 mg/day (n = 50) or famciclovir 500mg 3 times daily (n = 50) have been published in an abstract.[232] HBV DNA suppression occurred more rapidly and a greater proportion of lamivudine- than famciclovir-treated patients experienced a reduction of >2 $\log_{10}$ in HBV DNA levels or were HBV DNA negative (78 *vs* 8% $p < 0.0001$; LOD ≤2.5 pg/ml) after 12 weeks' of treatment.[232] Moreover, 45% of famciclovir recipients were nonresponders (HBV DNA levels decreased by <0.5 $\log_{10}$) at the end of treatment compared with only 2% of lamivudine-treated patients. Famciclovir recipients were switched to lamivudine 100 mg/day after 12 weeks; within 4 weeks HBV DNA levels had decreased by >2 $\log_{10}$ pg/ml or were undetectable in 76% of patients (i.e. a similar proportion to those treated with lamivudine in the first part of the study).[232] Although preliminary, these results suggest that lamivudine provides superior suppression of HBV DNA replication than famciclovir in patients with chronic hepatitis B. This finding is consistent with the results of *in vitro* studies in human cell lines (section 2.1.1).

4.2 Studies in Liver Transplant Candidates with Chronic Hepatitis B

Patients with chronic hepatitis B, end-stage liver disease and HBV DNA in serum are poor candidates for liver transplantation because of the high rate of recurrent hepatitis after transplantation.[7,233-235] In the absence of prophylactic treatment for hepatitis B recurrence, 80 to 90% of patients develop recurrent hepatitis B after liver transplantation.[236] In an attempt to improve outcomes after transplantation, lamivudine was administered alone[32,127,128,130] and in combination with HBIg[76,129,131-136] in nonblind, noncomparative studies in liver transplant candidates with HBV-associated end-stage liver disease. The use of lamivudine in this population has also been described in case reports and case series,[46,57,150,152,174,212,237,238] which are not discussed further.

Patients enrolled in these studies had chronic hepatitis B with decompensated cirrhosis and were positive for HBV DNA and/or HBeAg.[32,76,127-136] Patients with liver failure due to causes other than chronic hepatitis B[127] and those co-infected with hepatitis C (HCV) or D or HIV were excluded from 2 trials,[127,128] as were patients with a recent (i.e. ≤3 months[127]) history of antiviral therapy,[127] or those requiring retransplantation.[127]

Patients received oral lamivudine 100[32,76,127,128,134,136] or 150 mg/day.[129,131-133,135] The dosage of lamivudine was not stated in 1 report.[130] HBIg was administered during surgery and was continued for at least 6 months after transplantation. The duration of lamivudine therapy before transplantation was ≥2 weeks in studies that reported this parameter.[127-130,133] Lamivudine was started on the first day after transplantation in 1 study.[132]

When started before transplantation, lamivudine suppressed serum HBV DNA levels in most liver transplant candidates with chronic hepatitis B and end-stage liver disease (table V).[32,127-130,134,136] HBV DNA was not detected (by PCR) in post-transplantation liver biopsies in ≥64% of patients in 3 studies in which lamivudine was used alone (table V).[127,128,130] Moreover, HBcAg was absent from liver biopsy specimens in most of these patients.[127-130] These findings suggest that lamivudine protected the grafted liver from reinfection in some patients.

Lamivudine plus HBIg appears to be very effective in preventing reinfection of the grafted liver. In patients treated with lamivudine prior to transplantation and lamivudine plus HBIg after transplantation, no evidence of hepatitis B replication (e.g. HBV DNA, or HBeAg in serum) was evident in all but 2 patients for whom data is available (table V).[76,129,131] The dosage regimens for HBIg varied greatly in these trials: hence, further study

Table V. Effect of oral lamivudine (LAM) given before and after orthotopic liver transplantation in HBsAg-positive and/or HBV DNA-positive patients in nonblind, noncomparative studies

Reference	Baseline characteristics[a]		Regimen (duration of treatment after transplantation; wk)	Outcome (post-transplantation)[a]			
	HBV DNA+	HBeAg+		HBV DNA+	HBsAg+	HBeAg+	HBcAg+
Bain et al.[127]	4/4[b]	4/4	LAM 100 mg/day [12 to 104]	2/4[b]	2/4	2/4	2/4
Grellier et al.[128]	11/11[b]	3/11	LAM 100 mg/day [12 to 52]	3/11[b]	2/11	1/11	1/11
Van Thiel et al.[130]	4/4[c]		LAM [16 to 52]	0/4[b]	0/4[d]		0/4
Wright et al.[32] abstract	11/38[e]	18/37	LAM 100 mg/day [52]	0/34 (wk24)[e] 2/11 (wk52)	5/31 (wk24) 2/12 (wk52)	2/32 (wk24) 2/12 (wk52)	
Lamivudine in combination with hepatitis B immune globulin (HBIg)[f]							
Dodson et al.[132] abstract	1/5	1/5	LAM 150 mg/day plus HBIg [r = 20-52][g]		0/4[h]		
Han et al.[135] abstract			LAM 150 mg/day plus HBIg [m = 81; r = 31-138]		0/15		
Markowitz et al.[129]	5/14[i]	1/14	LAM 150 mg/day plus HBIg [r = 19-75]	0/13[jk]	0/13	0/13	0/2[l]
Marzano et al.[134] abstract	34/41	8/41	LAM 100 mg/day plus HBIg [m = 66]	0/31[m]	0/31	0/31	
McCaughan et al.[76] abstract	14/14		LAM 100 mg/day plus HBIg [md = 56]	0/14	0/14	0/14	
Roche et al.[136] abstract	15/15[c]	5/15	LAM 100 mg/day plus HBIg [r = 12-144]	1/15[n]	1/15		
Terrault et al.[131] abstract			LAM 150 mg/day plus HBIg [md = 55; r = 1-114]		0/23		
Yao et al.[133] abstract			LAM 150 mg/day plus HBIg [md = 36; r = 24-64]	1/10[o]	1/10		1/1[l]

a Number of patients with the characteristic/total number of patients.

b By PCR (LOD not stated).

c By branched DNA probe assay (LOD ≤2.5 pg/ml).

d By immunohistochemical staining of liver biopsy specimens from the grafted liver.

e HBV DNA assay not specified.

f In several studies,[129,131,132,135] patients received HBIg 10 000IU IV during the anhepatic phase, then 10 000IU daily for ≤7 days, and then once or twice monthly. After 6 months, the dosage of HBIg was reduced to 1000IU IM every 3 weeks in 1 study[132] and was discontinued in another study.[131] Marzano et al.[134] gave patients HBIg 42 000IU IV for 10 days, then 500IU IV every 2 days while in hospital, then 3000IU IV every 15 days. McCaughan et al.[76] gave patients HBIg 400IU daily for 1 week, then weekly for 1 month, then once per month. Roche et al.[136] gave patients HBIg to maintain an anti-HBs titre >500 IU/L. Yao et al.[133] gave patients HBIg 45ml IV daily for 7 days, then 5ml IM weekly for 1 month, then every 3 weeks.

g LAM was started on postoperative day 1.

h One patient died 1 month after transplantation due to technical complications.

i By dot-blot hybridisation (LOD ≤ 200 pg/ml).

j By PCR (LOD ≤ 100 copies/ml).

k One HBV DNA-negative, HBeAg-negative patient died 7 weeks after transplantation from complications of cardiac surgery.

l HBcAg immunohistochemistry was reported for 2 and 1 patients, respectively, in the studies by Markowitz et al.[129] and Yao et al.[133]

m 31 patients underwent liver transplantation.

n One patient, who was HBV DNA+ at the time of transplantation, died of acute hepatitis B recurrence 3 months after transplantation.

o Adequate anti-HBs titres were not achieved in 1 patient who developed recurrent hepatitis B 6 months after transplantation.

HBcAg+ = hepatitis B c antigen-positive by immunohistochemical staining in biopsy specimens taken from the grafted liver; **HBeAg**+ = hepatitis B e antigen-positive in serum; **HBIg** = hepatitis B immune globulin; **HBsAg** = hepatitis B surface antigen; **HBsAg**+ = HBsAg-positive in serum; **HBV DNA** = hepatitis B DNA; **HBV DNA**+ = HBV DNA-positive in serum; **IM** = intramuscular; **IV** = intravenous; **LOD** = limit of detection; **m** = mean; **md** = median; **PCR** = polymerase chain reaction; **r** = range.

is required to determined the optimal prophylactic dosage regimen in liver transplant recipients.

Preliminary evidence suggests that lamivudine may be an effective alternative to continued HBIg therapy in liver transplant recipients with no evidence of HBV after transplantation. In a nonblind study reported in an abstract, liver transplant recipients with no evidence of HBV recurrence 6 months after transplantation were randomised to 52 weeks' treatment with lamivudine 100 mg/day (i.e. HBIg was discontinued; n = 12), or continued HBIg prophylaxis (n = 12).[239] Of 21 patients completing the trial, all were HBsAg-negative and HBV DNA-negative in serum and were negative for HBcAg and HBsAg in liver biopsy specimens. Nonetheless, HBV DNA was detected by PCR in the serum of 6 lamivudine and 2 HBIg recipients after 52 weeks. Two lamivudine-treated patients, 1 of whom was HBV DNA-positive at baseline, and 1 HBIg recipient had HBV recurrences during the trial.[239]

Substitution of lamivudine for HBIg in 10 liver transplant recipients, all of whom remained HBsAg-negative 4 to 12 months after switching to lamivudine, was reported in a further abstract [the patients had been receiving prophylactic HBIg monotherapy for 2 (n = 1), 12 (n = 1) or ≥24 months (n = 8) prior to the switch].[240] Further study is needed to confirm these preliminary findings and to determine the optimal conditions for switching to lamivudine.

4.3 Studies in Patients with Recurrent Chronic Hepatitis B after Liver Transplantation

Lamivudine inhibits HBV replication and reduces the severity of liver disease in patients who develop chronic hepatitis B after liver transplantation. 52 HBsAg-positive, HBV DNA-positive liver transplant recipients with recurrent or *de novo* chronic hepatitis B received lamivudine 100 mg/day for 52 weeks in a multicentre, nonblind, noncomparative study (patients testing positive for HIV or HCV and those with aminotransferase levels >1500 IU/L were excluded).[74] At baseline, 87% (45 of 52) of patients were HBeAg-positive. After 52 weeks' treatment, 60% of patients (28 of 47) were HBV DNA-negative by solution hybridisation assay (LOD ≤1.6 pg/ml; in 5 patients HBV DNA was detectable only by PCR at baseline), 14 of 45 patients (31%) were HBeAg-negative (5 seroconverted to anti-HBe) and 3 patients (6%) had lost HBsAg (2 acquired anti-HBs).[74] Furthermore, between baseline and the end of treatment, mean ALT levels decreased from 116 IU/L to 67 IU/L ($p = 0.001$), bilirubin levels decreased significantly ($p = 0.001$) and albumin levels increased significantly ($p = 0.0001$ vs baseline).[74]

Hepatic necroinflammatory activity decreased with lamivudine treatment. The median total Knodell score decreased significantly after 24 weeks' treatment (from 10 to 6.5; $p = 0.003$), although the median score for fibrosis (3) was not changed.[74] 51% of patients had a reduction in necroinflammatory activity, defined as a reduction of ≤2 points in the Knodell necroinflammatory score; in 33% of patients there was no change and in 15% of patients necroinflammatory activity worsened during treatment.[74]

YMDD variant HBV was detected in 14 patients during the study. After the appearance of YMDD variant HBV, serum ALT levels increased in 11 patients, 5 of whom experienced clinical deterioration due to the progression of hepatic disease.[74]

4.4 Studies in HIV-Positive Patients with Chronic Hepatitis B

Lamivudine in combination with other antiretroviral agents may be useful in the management of HIV-positive patients with chronic hepatitis B. Lamivudine was evaluated in HIV-positive patients with chronic hepatitis B in a prospective, nonblind, noncomparative study.[140] The effect of lamivudine in this population was also studied by retrospective analysis of records from a study designed to assess the efficacy of lamivudine-based therapy in HIV infection (the CAESAR study).[142] In addition, the efficacy of lamivudine in hepatitis B-positive, HIV-positive patients has been re-

ported in case reports and case series which are not discussed further.[79,137-139,141,143-146,221]

Lamivudine suppressed HBV replication in HBsAg-positive patients with HIV co-infection.[140] After 52 weeks of lamivudine 300 or 600 mg/day, only 15% of patients with high rates of HBV replication and no patients with low rates of HBV replication prior to treatment had detectable HBV DNA levels in serum (by PCR; LOD <7 equivalent genomes per sample; table VI).[140] Five of 27 HBeAg-positive patients lost HBeAg during treatment, 3 of whom acquired anti-HBe. Moreover, 3 of 10 (30%) patients with low rates of HBV replication at baseline lost HBsAg during treatment, 2 of whom converted to anti-HBs.[140]

Retrospective analysis of the results of the CAESAR trial revealed that 27 of 66 (41%) lamivudine 300 mg/day recipients who were HBV DNA-positive at baseline became HBV DNA-negative (assay not described) compared with 18% (3 of 17) of placebo recipients at the end of the study (median duration of treatment was 52 weeks).[142,241] Further study is needed to determine the effect of lamivudine on other measures of disease activity (e.g. liver histology, ALT normalisation) in this population.

4.5 Dose Finding Studies in Children

Lamivudine suppressed HBV replication in children with chronic hepatitis B. Preliminary results from a dose finding study in paediatric patients with chronic hepatitis B have been published as an abstract.[113] In patients aged 2 to 12 years, lamivudine oral solution 0.7 to 8 mg/kg/day decreased HBV DNA levels by ≥99.5% after 4 weeks. A dosage of 3 mg/kg/day, approximately twice that used in adults with chronic hepatitis B, was considered optimal in children aged ≤12 years because this dosage produced maximal antiviral effects (99.9% inhibition of viral replication) and the AUC, C_{max} and C_{min} of lamivudine were similar to that seen in adults with chronic hepatitis B (section 3).[113]

5. Tolerability

The incidence of adverse events during 1 year was similar in Chinese patients treated with lamivudine 25 (77%) or 100 mg/day (80%) or placebo (77%) in a large (n = 358) study.[45] Adverse events that may have been related to lamivudine treatment, including diarrhoea, dizziness and nausea and vomiting, occurred in fewer than 17% of lamivudine recipients (fig. 10).[45] Abnormal liver function tests were more common in placebo (8%) than lamivudine 25 (4%) or 100 mg/day (2%) recipients.[45] No serious drug-related adverse events occurred during the study.

The frequency of adverse events in lamivudine- or placebo-treated patients was similar in a pooled analysis of 4 randomised, double-blind trials in patients with chronic hepatitis B and compensated liver disease (the Chinese study referred to above

Table VI. Effect of oral lamivudine 300 or 600 mg/day in HIV-positive individuals with chronic hepatitis B[140]a

Patient characteristics		Parameter (% of patients)				
		HBV DNA+	HBsAg+	HBeAg+	anti-HBe+	anti-HBs+
Patients with high rates of HBV replication (serum HBV DNA > 5 ng/L and HBeAg+)	Baseline (n = 30)	100	100	100	0	0
	Week 52 (n = 27)	15	100	81	11	0
Patients with low rates of HBV replication (serum HBV DNA < 5 ng/L and anti-HBe+)	Baseline (n = 10)	60	100	0	100	0
	Week 52 (n = 10)	0	70	0	100	20

a 10 patients received concomitant zidovudine 250 mg/day and 1 patient each received foscarnet and ganciclovir for cytomegalovirus infection.

anti-HBe+ anti-hepatitis B e antigen antibody-positive in serum; **anti-HBs**+ = anti-hepatitis B surface antigen antibody-positive in serum; **HBeAg**+ = hepatitis B e antigen-positive in serum; **HBsAg**+ = hepatitis B surface antigen-positive in serum; **HBV DNA**+ = hepatitis B virus DNA-positive in serum.

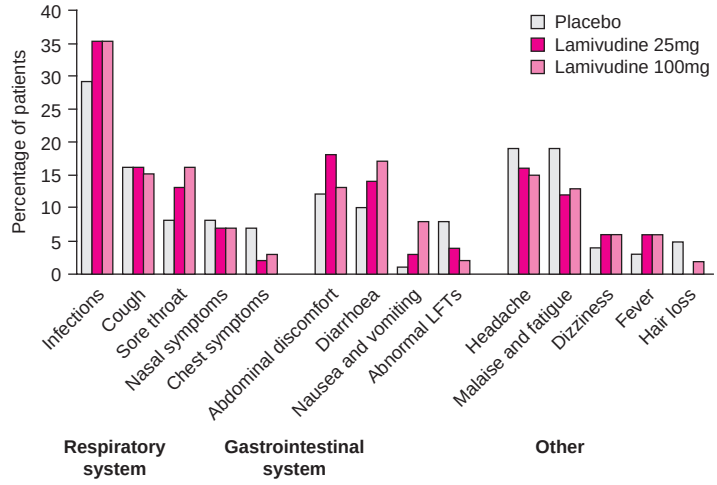

Fig. 10. Adverse events in patients receiving lamivudine for chronic hepatitis B. Frequency of adverse events during 52 weeks of treatment with lamivudine 100 (n = 143) or 25 mg/day (n = 142) or placebo (n = 72) in Chinese patients with chronic hepatitis B in a multicentre, randomised, double-blind study.[45] **LFT** = liver function tests.

was included in this analysis). One or more drug-related adverse events were reported by 40 and 45% of patients, respectively, treated with lamivudine 100 mg/day (n = 416) or placebo (n = 200) for 52 to 68 weeks in these trials.[242] Drug-related adverse events included malaise and fatigue, reported by 13 and 15% of lamivudine- or placebo-treated patients; nausea and vomiting in 8 and 9% of patients; headache in 9 and 11% of patients; diarrhoea in 6 and 4% of patients; and muscle pain in 4 and 5% of lamivudine and placebo recipients.[242] No deaths were reported during any of these studies.

Lamivudine was better tolerated than interferon-α (alone or in combination with lamivudine). In comparative trials the frequency of malaise and fatigue, headache, fever and chills, muscle pain, nausea and vomiting, hair loss or depressive disorders was 2 to 8 times more common in patients treated with interferon-α (alone or in combination with lamivudine) than lamivudine.[242] Abnormal liver function tests occurred in 10% of patients receiving lamivudine monotherapy, 14% of patients receiving interferon-α monotherapy and 9% of patients treated with lamivudine plus interferon-α.[242]

ALT levels have generally normalised in immunocompetent patients with chronic hepatitis B and compensated liver disease during treatment with lamivudine; however, substantial elevations in ALT levels have occurred, both during treatment and follow-up in patients treated with lamivudine or placebo. Grade 3 (3.1- to 10-fold increases over baseline) and 4 (>10-fold increases over baseline and/or evidence of hepatic failure) elevations in ALT levels occurred in 13% of patients treated with lamivudine 100 mg/day (n = 416) or placebo (n = 200) for 52 weeks.[242] The incidence of ALT elevations in immunocompetent patients with YMDD variant HBV was higher; 24% of patients with YMDD variant HBV experienced grade 3 or 4 elevations in ALT.[90] After discontinuation of therapy grade 3 and 4 elevations were documented in 19 (41 of 215) and 8% (5 of 66) of those treated with lamivudine or placebo, respectively (grade 4 elevations occurred in 3% and 2% of patients).[242]

Although post-treatment ALT elevations were more common in patients with chronic hepatitis B and compensated liver disease treated with lamivudine than placebo, ALT elevations generally resolved spontaneously and the incidence of hepatic decompensation was rare in both groups. Hepatic

decompensation, defined as a 2-fold increase in ALT levels over baseline and bilirubin levels 2 times the ULN and 2-fold greater than baseline, occurred in only 3 of 215 (1.4%) patients treated with lamivudine 100 mg/day and in 1 of 66 (1.5%) of placebo recipients.[242]

The frequency of clinically significant 'flare-ups' of hepatitis during treatment, or after discontinuation of lamivudine in immunocompetent patients with decompensated liver disease or in liver transplant recipients has not been described. However, because of the limited hepatic reserve in these patients, such flare-ups may be potentially serious.

The manufacturer advises that some fatalities have been reported in association with exacerbations of hepatitis after the acquisition of YMDD variant HBV or after discontinuation of lamivudine.[116]

6. Dosage and Administration

Lamivudine 100mg given once daily is the recommended dosage in patients with chronic hepatitis B with evidence of ongoing HBV replication, active liver inflammation and compensated liver disease.[116] In patients co-infected with HIV this dosage is inappropriate; such patients should receive lamivudine 150mg twice daily in combination with other antiretroviral agents.[116,243]

The use of lamivudine monotherapy at dosages recommended for chronic hepatitis B in patients with unrecognised or untreated HIV infection will promote the emergence of lamivudine-resistant HIV and limit treatment options for HIV. For these reasons, the manufacturer recommends that HIV counselling and testing be offered to all patients before beginning treatment and periodically during treatment with lamivudine for chronic hepatitis B.[116]

Lamivudine may be taken with or without food, so administration can be timed to accommodate the patient's schedule.

Elimination of lamivudine is altered in patients with renal dysfunction (see section 3) and dosage adjustments are recommended in patients with chronic hepatitis B and clinically significant renal dysfunction (table VII).[116] Lamivudine oral solution should be used to tailor the dosage to the needs of such patients. In patients undergoing intermittent haemodialysis (e.g. 2 or 3 times per week) no further dosage adjustments, in addition to those based on the Cl_{cr}, are required.

Lamivudine pharmacokinetics are not affected significantly by hepatic dysfunction; therefore, dosage adjustments are not required in patients with hepatic dysfunction unless accompanied by renal impairment.

Before initiating treatment, during lamivudine therapy and for several months after discontinuation of the drug, patients should be monitored closely. An increase in HBV DNA and/or ALT levels after initial decreases in these parameters, progression of the clinical signs or symptoms of hepatic disease, and/or worsening of necroinflammatory activity may indicate a reduced therapeutic response to lamivudine during treatment, or may portend a post-treatment exacerbation if the drug has recently been discontinued.[116]

The safety and efficacy of lamivudine have not been established in patients with decompensated liver disease, in children or during pregnancy.[116]

7. Place of Lamivudine in the Management of Chronic Hepatitis B

The World Health Organization estimates that more than 350 million people, 75% of whom reside

Table VII. Lamivudine dosage recommendations in patients with chronic hepatitis B and renal dysfunction[116]

Cl_{cr} (ml/min)[a]	First dose[b]	Daily maintenance dose[bc]
ô50	No dosage adjustment required	
<50 ≥30	100mg (20ml)	50mg (10ml)
<30 ≥15	100mg (20ml)	25mg[c] (5ml)
<15 ≥5	35mg (7ml)	15mg (3ml)
<5	35mg (7ml)	10mg (2ml)

a An estimate of Cl_{cr} may be obtained with the formula derived by Cockroft and Gault:[244]
Cl_{cr} = [(140 - age) • (weight in kg)] / [0.81 • S_{cr} in μmol/L]. In females multiply the result by 0.85. To convert to L/hr multiply by 0.06.

b Lamivudine 5 mg/ml oral solution given once daily.

c In HIV-positive patients the recommended daily maintenance dosage is 100mg if the Cl_{cr} is <30 ≥15, 50mg if the Cl_{cr} is <15 ≥5 and 25mg if the Cl_{cr} is <5.[243]

Cl_{cr} = creatinine clearance.

in Asia, are chronically infected with HBV.[4,245] In the US, 5000 to 30 000 people become chronically infected each year, adding to the estimated 1.25 million existing cases of chronic hepatitis B in that country.[10,246,247] In patients with chronic hepatitis B and evidence of active viral replication, the 5-year incidence of cirrhosis is 15 to 20%.[248]

Individuals with chronic hepatitis B may develop hepatocellular carcinoma after a latency period of 10 to 30 years.[247] The risk of hepatocellular carcinoma in patients with chronic hepatitis B is much greater – perhaps 200- to 300-fold greater[6] – than that in the general population.[5] Indeed, in men and women who acquire HBV at birth, the lifetime risk of hepatocellular carcinoma is 50 and 20%, respectively.[249] More than 600 000 deaths were attributed to hepatitis B in 1997.[250]

Effective vaccines are available and prevention of chronic hepatitis B and its sequelae is possible.[251,252] The advent of universal vaccination programmes in newborns and adolescents will reduce the prevalence of chronic hepatitis B and liver cancer and, if virus transmission can be interrupted, may eventually result in eradication of the virus.[10,251,253,254] Nonetheless, new infections are common and, given the prevalence of chronic hepatitis B, many millions of people would benefit from effective therapy for the disease.

Interferon-α has been used extensively in patients with chronic hepatitis B. A significant proportion of patients experience ALT normalisation and become HBV DNA-negative and HBeAg-negative after treatment with interferon-α.[255,256] A meta-analysis of 15 controlled studies showed that approximately one-third of patients lose HBeAg as a result of a 3- to 6-month course of interferon-α compared with 12% of placebo recipients.[257] Loss of HBeAg in response to therapy with interferon-α results in a lower incidence of liver failure, cirrhosis and the need for liver transplantation.[258] The drug increases HBsAg seroconversion rates, increases life expectancy and is cost effective compared with standard care in patients who do not have cirrhosis.[246,259] In patients with chronic hepatitis B and cirrhosis, interferon-α lowers the incidence of hepatocellular carcinoma and liver-related death.[260] Patients most likely to respond to a course of interferon-α are immunocompetent, have low HBV DNA levels of an HBeAg-producing viral strain and have active liver disease (characterised by high aminotransferase levels and evidence of fibrosis) of short duration.[261] Patients harbouring precore mutant HBV strains (HBeAg-negative, HBV DNA-positive), which are more prevalent in Asia, Africa and the European Mediterranean region than elsewhere, generally do not respond well to therapy with interferon-α.[227] Although effective in a subset of patients, parenteral administration of interferon-α is inconvenient, the drug is not well tolerated and it is expensive. Approximately 20% of patients require dosage reductions and 5 to 10% discontinue interferon-α therapy because of adverse events (common adverse events include headache, fatigue, myalgia, nausea and vomiting, hair loss, neutropenia and depression).[261]

A functional immune system is a prerequisite to therapeutic efficacy with interferon-α.[261] Hence, immunosuppressed patients with chronic hepatitis B derive less benefit from interferon-α than immunocompetent patients.[261,262] The attenuation of cell-mediated immunity and the presence of a glucocorticoid responsive element in the HBV genome may contribute to the reduced efficacy of interferon-α in this population.[263] Moreover, interferon-α may precipitate rejection in allograft recipients.[140,261,262,264-266]

Lamivudine inhibits replication of HBV by interfering with viral DNA polymerase. Accordingly, its mechanism of action differs from that of interferon-α. The outcome of prior treatment with interferon-α had no effect on the efficacy of lamivudine. Most patients experienced profound reductions in HBV DNA levels while receiving lamivudine. Moreover, clinically meaningful improvements in liver histology and normalisation of ALT levels were significantly more common in lamivudine than placebo recipients in several randomised controlled trials in patients with ongoing viral replication,[45,122] including HBeAg-negative

patients – a group that generally does not respond well to interferon-α.[126]

Within 1 year of starting treatment with lamivudine, clinically significant improvements in liver histology were evident in a large proportion of patients.[45,122,126] Hepatic necroinflammatory activity was attenuated in patients receiving lamivudine and the progression of hepatic fibrosis was halted or reversed. Hepatic fibrosis ultimately results in cirrhosis, so the ability of lamivudine to arrest the progression of fibrosis is important. Whether long term suppression of viral replication with lamivudine will prevent cirrhosis or hepatocellular carcinoma, reduce the need for liver transplantation and/or prolong life, remains to be determined in long term studies.

The frequency of HBeAg seroconversion increased significantly during treatment with lamivudine. Seroconversion rates at the end of treatment were 2.8-fold (17 *vs* 6%)[122] and 4-fold (16 *vs* 4%)[45] greater in lamivudine- than placebo-treated patients in 1-year studies. Nonetheless, the long term durability of HBeAg seroconversion after withdrawal of lamivudine is unknown.

In patients with chronic hepatitis B and ongoing viral replication, seroconversion from HBeAg-positive to positive for antibodies to HBeAg (anti-HBe) is significantly associated with improved clinical outcomes including survival.[258,267] The annual rate of seroconversion from HBeAg-positive to anti-HBe was estimated to be 13.4 and 16%, respectively, in surveys of untreated Chinese[268] and Italian patients.[269] HBeAg seroconversion is usually associated with biochemical and histological regression of inflammatory activity,[269] so the finding that lamivudine enhances seroconversion is of clinical significance. In another survey, the frequency of conversion from HBsAg-positive to positive for antibodies to HBsAg (anti-HBs) was estimated to be 1.7%.[270] There is no evidence at present that lamivudine influences HBsAg seroconversion in patients with chronic hepatitis B.

Liver transplantation in patients with evidence of viral replication is associated with a significant risk of reinfection.[235,262,264] Indeed, in 1 series of patients receiving liver transplants for chronic hepatitis B, 83% who were HBV DNA-positive at the time of transplantation became HBsAg-positive after transplantation, compared with 58% who were both HBV DNA- and HBeAg-negative at the time of transplantation.[271] Recurrent chronic hepatitis B is associated with high rates of graft loss and a low probability of survival. For example, in the study cited above,[271] the 3-year survival rate in patients with recurrent infection after liver transplantation was 54% compared with 83% in patients who remained HBsAg-negative after transplantation. Although the advent of passive immunisation with HBIg has significantly reduced the rate of reinfection,[235,271] and improved survival in liver transplant recipients,[272] reinfection remains a substantial problem (reported to occur in up to 42% of patients[235]) and HBIg is expensive, in short supply and may predispose patients to mercury toxicity.[129,235,264] Lamivudine suppresses HBV replication in immunocompromised patients and limited data suggest that, when started prior to transplantation, it may prevent reinfection of the graft (indicated by the absence of HBsAg in serum and HBcAg and HBV DNA in liver biopsy specimens) in some liver transplant recipients. Indeed, it has recently been suggested that lamivudine be given for at least 1 month before liver transplantation in patients at risk of reinfection.[262]

The pharmacological effects of lamivudine and HBIg complement each other in liver transplant recipients. By inhibiting HBV replication, lamivudine may reduce the likelihood of the binding capacity of HBIg becoming overwhelmed by viral antigens.[129] Furthermore, lamivudine is unlikely to select for HBIg-resistant mutations in HBsAg.[129] Passive immunisation with HBIg, in turn, may confine the virus to extrahepatic sites and, through maintenance of a low viral load, may lower the probability of lamivudine-resistant mutations arising.[129] The results of several small, noncomparative studies, in which graft reinfection or lamivudine resistance was largely prevented in liver transplant recipients given lamivudine plus HBIg, are encouraging. Whether the frequency of

recurrent chronic hepatitis B and the dose, duration and hence, expense associated with HBIg prophylaxis can be reduced through combination therapy with lamivudine remains to be determined.

Chronic hepatitis B is a significant problem in HIV-positive individuals. The combined prevalence of current or past infection with HBV was 84% in 1 survey of 511 HIV-positive individuals,[273] and the frequency of HBsAg positivity is approximately 5 to 10% in this population.[273-276] Furthermore, loss of HBeAg occurs at a lower rate than in the general population.[277] With the advent of highly effective antiretroviral combination therapy which prolongs life in HIV-positive patients, therapy for chronic hepatitis B may become more important in this population.[10] Lamivudine reduced HBV replication in HIV-positive patients. Moreover, lamivudine-based therapy has resulted in reduced progression to AIDS and reduced mortality in HIV-positive patients.[241] The drug is well tolerated and does not predispose HIV-positive patients, in whom polypharmacy is common, to drug interactions. Nonetheless, the decision to use lamivudine in HIV-positive patients with chronic hepatitis B must be guided by patterns of resistance and cross-resistance of both HIV and HBV.

Lamivudine-resistant HBV emerges in some patients with chronic hepatitis B during treatment with lamivudine. Optimal management strategies for these patients have yet to be developed through prospective, controlled clinical trials. Strategies to minimise resistance to lamivudine such as combination therapy with other antiviral agents, an approach which has been very effective in the treatment of HIV infection, remain to be explored.[82,278,279]

In contrast to interferon-α, lamivudine is well tolerated in patients with chronic hepatitis B. Withdrawal rates were low in all populations in which the drug has been tested and it has not been causally associated with serious adverse events or clinically significant drug interactions. Although serious elevations in ALT levels have been documented, both during treatment and after discontinuation of lamivudine in clinical trials, ALT elevations generally resolved spontaneously and hepatic decompensation was rare in patients with compensated liver disease.

In conclusion, lamivudine profoundly inhibits HBV replication in patients with chronic hepatitis B regardless of ethnic group, the mode of acquisition of the virus, or the presence of wild type or precore mutant HBV. The drug reduces hepatic necroinflammatory activity and the progression of fibrosis in patients with chronic hepatitis B, ongoing viral replication and compensated liver disease. Lamivudine also suppresses viral replication in liver transplant recipients and HIV-positive patients. The drug is well tolerated and is not involved in any clinically significant drug-drug interactions. Thus, lamivudine is potentially useful in a wide range of patients with chronic hepatitis B and ongoing viral replication.

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