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A Preliminary Benefit-Risk Assessment of Lamivudine for the Treatment of Chronic Hepatitis B Virus Infection

Fabien Zoulim

INSERM Unit 271, Lyon, France

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Abstract

Chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide. Until recently, interferon (IFN)-α was the only approved drug for the treatment of chronic HBV infection. The recent registration of lamivudine, a dideoxycytidine analogue that inhibits both the HIV and HBV reverse transcriptases, has provided new perspectives for the treatment of chronic HBV infection. Lamivudine treatment for 12 months leads to a control of viral replication during therapy in the majority of the patients and to sustained anti-hepatitis B e (anti-HBe) seroconversion in 16 to 22% of the patients, associated with a biochemical and histological response. Further studies showed that extended lamivudine therapy increases the rate of anti-HBe seroconversion. However, long-term therapy is associated with the progressive emergence of drug resistant mutants. In most cases these mutants are not associated with a deterioration of the liver disease within the available follow-up. In the remaining patients and in particular settings such as liver transplantation, a severe exacerbation of the liver

disease is observed and that requires add-on therapy. Lamivudine treatment of patients infected with a pre-core mutant also showed beneficial effect with the control of viral replication, and a biochemical and histological response in approximately 60% of the patients at 1 year. These patients face the same problem of drug resistant mutants, and the optimal duration of lamivudine treatment still needs to be determined in this clinical situation. Moreover, lamivudine therapy is the only therapeutic option in decompensated cirrhotic patients to allow liver transplantation, and in liver transplant patients with HBV recurrence following transplantation. Adverse effects of lamivudine therapy are comparable to those observed in placebo-treated patients. ALT flares have been observed mainly in relation to the re-occurrence of viral replication due to the rebound of viral replication after therapy withdrawal, or to the emergence of drug resistance mutants. Therefore, lamivudine provides a new treatment alternative for patients with chronic HBV infection. For each patient, its indication has to be weighed against the risk of developing viral resistance but also against the risk of natural history of the disease.

Hepatitis B virus (HBV) continues to pose major health problems worldwide. Despite the availability of efficient vaccines, 400 million people remain chronically infected, i.e. 5% of the world's population.[1] These chronic carriers mainly live in Asia and in Africa. In the European Union there are 4 million chronic carriers and in eastern European countries their number exceeds 15 million. The economic burden imposed by HBV infection is substantial. A recent evaluation revealed that direct medical costs and work-loss costs consumed up to 0.5% of the total German healthcare budget (Deutschmark 247 billion) in 1997. Indeed it has been estimated that 10 to 15% of these carriers may ultimately develop cirrhosis or hepatocellular carcinoma. In the setting of routine clinical work in a liver department, the prevalence of cirrhosis in patients with chronic HBV infection may be as high as 30%.[2,3] The WHO estimated that HBV infection is the ninth leading cause of death worldwide.[1]

The first approved treatment for chronic HBV infection was interferon (IFN)-α. Several meta-analysis of clinical trials showed a higher rate of hepatitis B e antigen (HBeAg) and HBV DNA loss in patients treated with IFNα and this is accompanied by a decrease in ALT levels, a remission in the liver disease and an improvement in survival and clinical outcome, compared with the untreated patients.[4,5] The efficacy of IFNα is decreased in patients with vertically acquired HBV infection, in patients with pre-core mutant infection, and in patients in the immune tolerance phase. Moreover, IFNα is expensive and is associated with significant adverse effects including a flu-like syndrome, depression, asthenia, bone marrow suppression and autoimmune disorders.[4] The use of IFNα is also limited by the need for parenteral administration and the fact that is it contraindicated in patients with decompensated liver disease and in the setting of organ transplantation.

Lamivudine, an inhibitor of the HBV reverse transcriptase activity, has been approved recently for the treatment of chronic HBV infection in many countries worldwide.[4] It has been evaluated in more than 900 patients in clinical trials. Examination of viral markers showed a decrease in viral DNA titres, HBeAg seroconversion and a decrease in liver histology activity index in a significantly higher number of patients compared with placebo recipients. In these studies no signs of mitochondrial toxicity nor of bone marrow suppression were observed.

Here, an analysis of the published results of the

main phase III trials and other clinical studies is presented in terms of a benefit-risk assessment.

1. Natural History of Hepatitis B Virus Infection

The mechanism of liver cell injury in patients with HBV infection has not been entirely elucidated. While most evidence suggests that HBV is not directly cytopathic, liver cell injury is likely mediated by cytotoxic T cell immunity. The onset of the disease is generally mild since most patients have asymptomatic initial presentations, and the vast majority of them recover completely. However, 2 to 5% of adult patients with acute HBV infection and 90% of the exposed neonates or infants below the age of 3 years become chronic carriers of hepatitis B surface antigen (HBsAg) – characterised by HBsAg carriage for more than 6 months – who subsequently are at risk for developing chronic hepatitis, cirrhosis and primary hepatic cancer (also known as hepatocellular carcinoma). As mother to baby, and transmission to infants are the leading transmission routes in the endemic areas, i.e. Asia and Africa, leading to a high rate of chronicity, HBV infection is a major public health problem worldwide.[1]

In wild-type HBV chronic infections, three stages characterise the progression of liver disease in immunocompetent individuals, possibly leading to advanced liver disease with cirrhosis and its complications.[6,7] The first stage, lasting from 1 to 15 years, is characterised by an immunotolerant state with high HBV replication levels and low grade inflammatory lesions in the liver. The second stage, lasting from a few weeks to months, is characterised by clearance of infected hepatocytes with an increase of hepatocyte necrosis and serum aminotransferase levels, decrease of serum HBV DNA level followed by seroconversion of HBeAg to anti-HBe. Loss of serum HBV DNA [identified by non-polymerase chain reaction (PCR)-based methods] may occur spontaneously in about 5 to 10% of patients yearly or as a result of antiviral therapy. If this stage does not progress rapidly to HBeAg seroconversion, antiviral therapy is mandatory to block viral replication, induce anti-HBe seroconversion and remission of the liver disease. The seroconversion from replicative to nonreplicative chronic HBV infection is usually associated with clinical improvement. However, it may be clinically silent or accompanied by a transient clinical exacerbation. Severe liver lesions develop mainly during the second stage, the third stage being characterised by a rather low HBV replication level (serum HBV DNA detectable by sensitive PCR-based methods only), the persistence of integrated HBV DNA in the host genome and disappearance of hepatic necro-inflammatory lesions while cirrhosis may have already developed.

Interestingly, 15 to 80% of patients with chronic HBV infection are infected with a pre-core mutant virus.[2,8-10] This is characterised by the absence of HBeAg and presence of anti-HBe in serum, in association with active virus replication (presence of circulating HBV DNA in serum). Most often, these mutants arise during the natural course of wild-type chronic HBV infection and are selected by the anti-HBe immune response. Pre-core mutant virus-induced infections, characterised by fluctuations of serum HBV DNA and aminotransferase levels, are often associated with severe evolution of liver disease, leading to cirrhosis in up to 40% of patients.

The inactive HBsAg carrier state corresponds to asymptomatic patients who are clinically well, who have normal aminotransferase levels and evidence of HBsAg in their serum, associated with anti-HBe antibody and low levels of HBV DNA ($<10^4$ copies/ml).[6] The prognosis of such patients over time is excellent unless they show evidence of clinical or laboratory exacerbations, which may place them at risk for the development of cirrhosis.[11] They are usually not candidates for antiviral therapy.[7] However, they remain at risk for hepatocellular carcinoma because of HBV genome integration, albeit at much lower rate than those patients with chronic hepatitis and cirrhosis. They should be considered for hepatoma surveillance

along with a basic clinical and laboratory evaluation on a yearly basis or at any time that symptoms suggestive of liver disease are present.

2. Clinical Efficacy of Lamivudine Therapy

A total of 950 patients were involved in the key phase III studies, 825 HBeAg positive patients[12-15] and 125 HBeAg negative patients,[16] including treatment-naive patients[12,13,16] and non-responders to IFNα.[15] Most trials examined the efficacy of lamivudine monotherapy, while only two reported results with the combination of lamivudine plus IFNα.[15]

2.1 Wild Type Virus Infection

Lamivudine administration at a daily dose of 100mg is associated with a significant suppression of serum HBV DNA (3 log decrease). In two phase III placebo controlled trials including nearly 500 patients who were HBeAg and who had elevated transaminase levels,[12,13] 12 months of lamivudine therapy was associated with a decrease in HBV DNA to an undetectable level using hybridisation techniques in most of the patients. The rate of suppression of HBV to undetectable level in different trials varied according to the type of assays used. In patients receiving lamivudine monotherapy or placebo the following changes were observed: anti-HBe seroconversion 16 to 17% versus 4 to 6%, respectively; transaminase level normalisation 41 to 72% versus 7 to 24%, respectively; liver histology improvement in 56 versus 25%, respectively (table I). Another study involving 23 patients included in a phase II trial showed that the initial decline of HBV DNA below 10^4 copies/ml was associated with a significantly higher rate of seroconversion and lower rate of drug resistance.[17] These results that were obtained while patients were receiving lamivudine therapy are comparable to those observed 6 months after the cessation of IFNα therapy.[5,18]

The effect of extended therapy with lamivudine was analysed in a subgroup of patients who were initially enrolled in the 12 month trial of lamivudine.[12] There was an increase in anti-HBe seroconversion rate over time: 17 to 22% at 1 year, 27 to 29% at 2 years, and 40% at 3 years.[19,20] This

Table I. Biochemical and virological response during lamivudine mono- or combination therapy

Study	Number of patients	Treatment	Patients with Anti-HBe seroconversion (%)	Patients with normal ALT levels (%)
Year 1				
Lai et al.[12]	358	Lamivudine monotherapy	16 (*vs* 4 with placebo)	72 (*vs* 24 with placebo)
Dienstag et al.[13]	137	Lamivudine monotherapy	17 (*vs* 6 with placebo)	41 (*vs* 7 with placebo)
Liaw et al.[19]a	93	Lamivudine monotherapy	17	37.5
Leung et al.[20]a	58	Lamivudine monotherapy	22	38
Schalm et al.[14]	75	Lamivudine + IFNα	29	38
	69	IFNα monotherapy	19	29
	82	Lamivudine monotherapy	18	57
Year 2				
Liaw et al.[19]a	93	Lamivudine monotherapy	27	47.5
Leung et al.[20]a	58	Lamivudine monotherapy	29	42
Year 3				
Leung et al.[20]a	58	Lamivudine monotherapy	40	65

a Patients enrolled in Leung et al.[20] and Liaw et al.[19] represent a subgroup of patients who received extended lamivudine therapy following the initial evaluation of 12-month lamivudine therapy in a larger group of patients described in Lai et al.[12]

Anti-HBe = anti-hepatitis B e antigen; **IFNα** = interferon-α.

indicates that long-term lamivudine therapy is required in the majority of the patients in order to obtain anti-HBe seroconversion. However, as no control group was included in these studies after the first year of therapy, it is not possible to determine whether this increased rate of anti-HBe seroconversion is due to lamivudine administration or to spontaneous immune clearance after the first year.

Among the predictors of response that were studied, the best is the pre-treatment aminotransferase level. Among patients with transaminase levels higher than two times the upper limit of normal, anti-HBe seroconversion increases from 37.5 to 38% at year one, 42 to 47.5% at year two, and 65% at year three.[19-21] This also indicates that anti-HBe seroconversion is unlikely in patients with normal aminotransferase levels at baseline. Anti-HBe seroconversion is sustained in approximatively 75% of these patients. It will be interesting to determine the long-term outcome of these patients after lamivudine withdrawal and compare it to the IFNα-treated patients.[22]

From the results of these clinical trials, mathematical models were applied to determine the kinetics of viral clearance. These studies demonstrated that long-term lamivudine treatment is required to control or eradicate HBV infection.[23] This then places the patient at risk of developing resistance to lamivudine by the selection of polymerase mutants that are resistant to this nucleoside analogue.[24] It remains therefore to determine the benefit-risk for those patients who failed to seroconvert and require long-term treatment.

The efficacy of the combination of lamivudine and IFNα was compared with that of both agents given as monotherapies in a randomised trial, involving 230 patients.[14] The patients receiving the combination treatment received lamivudine 100 mg/day for 24 weeks and IFNα 10MU three times weekly for 16 weeks, starting 8 weeks after lamivudine therapy was started. Lamivudine monotherapy was administered for 52 weeks and IFNα monotherapy for 16 weeks. The rate of anti-HBe seroconversion at week 52 was 29% in the combination group, 19% for IFNα monotherapy, and 18% for lamivudine monotherapy. The rate of lamivudine-induced anti-HBe seroconversion was similar to that of IFNα alone.[5,18,25] However, the difference in favour of the combination treatment did not reach statistical significance. In the per protocol analysis the rate of anti-HBe seroconversion was two times higher in the combination group than in patients receiving lamivudine monotherapy ($p = 0.02$). Another recently published study using high doses of IFNα and lamivudine showed a higher anti-HBe seroconversion rate in the combination group versus lamivudine monotherapy.[26] The results of this study indicates that the potential benefit of combining lamivudine and IFNα warrants further investigations using different regimens of combination therapy based on the better knowledge of the restoration of the anti-HBV cellular immune response in patients treated with lamivudine alone.[27,28] Indeed, other studies of the IFNα plus lamivudine combination did not show a significant benefit of the combination over IFNα monotherapy, especially in previous patients who have previously not responded to IFNα,[29] while a recent pilot study of sequential lamivudine followed by IFNα treatment showed a high rate of anti-HBe seroconversion in patients who had previously not responded to IFNα monotherapy.[30] New trials are clearly needed to find the optimal schedule and regimen of the IFNα plus lamivudine combination.

2.2 Pre-Core Mutant infection

In patients with a pre-core mutant infection, the classical endpoint, i.e. anti-HBe seroconversion, is not valid anymore. Furthermore, the assessment of treatment efficacy is difficult as the natural history of the disease is characterised by a spontaneous fluctuation of ALT levels and HBV DNA load. The usual criteria of treatment efficacy are the loss of detectable HBV DNA in serum, normalisation of ALT levels, and improvement of liver histology. IFNα therapy usually leads to a sustained virolog-

ical and biochemical response in only 20 to 30% of the patients.[31,32]

In a placebo-controlled trial including 125 patients, 63% of the lamivudine-treated patients presented a complete virological and biochemical response at month 6, compared with 6% in the placebo group.[16] At week 52, 65% of the lamivudine-treated patients remained complete responders, but there was no comparator group at this time point. The liver necro-inflammatory score improved in 60% of the patients with a second liver biopsy at week 52.

In an open label study of 25 patients,[33] the rate of biochemical response was 88% at month 6, 96% at month 12, 68% at month 18, 59.5% at month 24, and 42.5% at >30 months. The virological response rate was 68% at month 6 and 12, 52% at month 18, and 41.6% at both month 24 and ≥30 months. In another study of 29 patients[34] the rate of virological response was 69% at month 6 and 60% at month 24.

Despite the fact that pre-core mutant HBV infection represents a high proportion of the patients with chronic hepatitis B,[2,35] these data have been obtained from a relatively small number of patients. Overall, the results indicate that the initial response to lamivudine therapy is good during the first year of therapy, but that virological breakthrough becomes significant after a year of treatment (table II). Moreover, only a small amount of data is available on the outcome of viral infection after cessation of lamivudine. It is clearly mandatory to get more information on the optimal duration of lamivudine treatment in this group of patients. Another unresolved issue is the optimal timing to start antiviral treatment.[36] These issues are especially important to answer as a recent study showed that a sustained response was observed in only 18% of patients with pre-core mutant HBV infection who received either one course of IFNα therapy or were re-treated with IFNα if there was no initial response or if there was a relapse.[37] At this stage, it would be very important to obtain information, in a large cohort of patients, on the sustained response rate after cessation of lamivudine therapy and on the rate of drug resistance, to compare its benefit to that of IFNα.

2.3 Patients with Decompensated Cirrhosis

The prognosis of decompensated liver cirrhosis resulting from chronic HBV infection is poor. In this situation, IFNα therapy is difficult due to the high risk of serious adverse effects and the risk of fatal exacerbation of disease activity. It can be performed only in specialised centres using low doses of IFNα with a careful clinical monitoring.[38] Three main studies involving 66 patients in total showed the benefit of lamivudine treatment (table III). In the first study[39] seven of 35 patients underwent liver transplantation within 6 months after treatment initiation, five patients died, and 23 patients were treated for more than 6 months. In these latter patients, serum bilirubin levels decreased significantly, albumin levels increased and Child-Pugh score decreased significantly. Liver function improvement was slow but concomitant with the control of viral replication. The other two studies,[40,41] involving 13 and 18 patients, confirmed that lamivudine therapy appears highly effective in controlling viral replication and in improving liver functions in this serious clinical situation. Nine of 20 patients who were considered

Table II. Virological response (percentage of patients) during lamivudine therapy for chronic hepatitis B virus (HBV) infection associated with pre-core mutant HBV infection

Study	No. of patients	Month 6	Month 12	Month 18	Month 24	Month ≥30
Tassopoulos et al.[16]	125	63 (*vs* 6 with placebo)	65			
Hadzyiannis et al.[33]	25	68	68	52	41.6	41.6
Lok et al.[34]	29	69			60	

Table III. Virological response and viral breakthrough during lamivudine therapy of hepatitis B virus (HBV) infection–associated liver cirrhosis

Study	No. of patients	HBV DNA suppression at month 6	Viral breakthrough
Villeneuve et al.[39]	35	23/23 [a]	3/23[a]
Yao and Bass[40]	13	13/13	1/13
Kapoor et al.[41]	18	18/18	3/18

a Twenty-three of the initial 35 patients were treated for >6 months.

for liver transplantation were removed from the waiting list because of the improvement of their liver function.

However, one should be cautious as these dramatic results were obtained in a relatively small number of patients included in uncontrolled studies. Furthermore, the removal of some these patients from the waiting list and the requirement for prolonged therapy to maintain stable liver function may place these patients at risk for the development of viral resistance which may in turn lead to later clinical deterioration. It may be difficult then to determine the optimal timing for liver transplantation in patients who maintain stable liver function with lamivudine therapy. This problem may be solved in part when new antiviral drugs, such as adefovir,[42,43] that inhibit lamivudine-resistant mutants as well as wild type virus become clinically available.[42] Adefovir is now available in many countries in open label trials or in the setting of compassionate use programmes.

2.4 Liver Transplantation

2.4.1 Therapy of Hepatitis B after Liver Transplantation

Recurrence of hepatitis B after liver transplantation or *de novo* HBV infection after organ transplantation may lead to rapid and severe disease progression followed by loss of graft function within the first years following liver transplantation. IFNα therapy is poorly effective in this situation because of the concomitant immunosuppressive therapy and the subsequent high levels of viral replication. Furthermore, IFNα is usually poorly tolerated in patients with a liver transplant and should be used with extreme caution because of an increased risk of organ rejection. In one open label, non-randomised study,[44] 52 patients with hepatitis B post-transplant received lamivudine therapy for 52 weeks. Control of viral replication was achieved in 60% of the patients (undetectable HBV DNA), 31% lost HBeAg, 6% lost HBsAg. Serum ALT normalised in 71% patients, albumin and bilirubin levels improved, and the histological activity index decreased significantly. Drug resistance developed in 27% of patients, but eight of 14 did not present clinical deterioration. Altogether, these data suggest that lamivudine provides a new treatment option in this serious clinical situation that was previously considered as a therapeutic dead-end.

2.4.2 Prophylaxis against Hepatitis B Recurrence after Liver Transplantation

The advent of long-term anti-HBs immunoglobulin (HBIG) administration as a prophylaxis of HBV recurrence has been a major advance in the management of liver transplantation for HBV infection. HBV recurrence has been reduced to 20 to 35% in cirrhotic patients with HBV infection and low level viral replication pre-transplant, but has remained high, 30 to 80% in cirrhotic patients with HBV infection and high HBV replication.[45] The drawbacks of HBIG administration are the cost of the long-term administration, the need for a close monitoring to adapt the frequency of readministration depending on the anti-HBs levels, and the high recurrence rate in patients with high HBV replication levels.

As lamivudine is well tolerated and controls viral replication in cirrhotic patients, attempts to

prevent HBV recurrence were made using lamivudine monotherapy pre and post-transplant.[46] However, an overall recurrence rate of 40% was observed in a recent multicentre study.[47] Several groups have developed a strategy that combines lamivudine monotherapy pre-transplant to lower viral load and lamivudine plus HBIG post-transplant. In these studies the HBV recurrence rate was less than 20%,[48,49] and the need for HBIG was reduced most likely by a decreased production of HBsAg. These studies clearly indicate that the latter approach is more effective in preventing HBV recurrence, but the optimal duration of prophylaxis remains to be determined. Furthermore, by controlling viral replication with lamivudine pre-transplant, it is now possible to transplant those cirrhotic patients with high HBV replication who were previously removed from the waiting list. An interesting study has shown that in patients with HBIG prophylaxis alone and low HBV replication, the substitution of HBIG by lamivudine administration is equally effective at one year.[50] The long-term outcome of these patients needs to be studied as well as the optimal protocol of prophylaxis needs to be determined before changing the currently validated protocols.

2.5 Co-Infection with Hepatitis D Virus or HIV

Lamivudine therapy was evaluated in patients infected with both HBV and hepatitis D virus (HDV). Although lamivudine inhibited HBV replication, it did not inhibit HDV replication nor did it improve liver disease activity.[51] Lamivudine monotherapy should therefore not be considered for treatment of chronic HDV infection.

As lamivudine inhibits both HIV and HBV reverse transcriptases, it was expected that its administration in HIV-positive patients co-infected with HBV may inhibit HBV replication.[52,53] Most studies showed that lamivudine administered at 300 mg/day for HIV inhibits HBV replication in the majority of the patients. However, the same issue of prolonged therapy appears with the progressive selection of drug resistant mutants.

3. Clinical Safety of Lamivudine Therapy

3.1 Clinical and Biological Adverse Events

The following data regarding adverse effects are pooled from the four phase III studies.[12-15] In the four phase III trials of lamivudine therapy for HBeAg positive chronic HBV infection, the incidence of adverse events was significantly higher ($p < 0.001$) among patients receiving lamivudine plus IFNα (96%) and IFNα monotherapy (99%) compared with lamivudine alone (86%), which was not significantly different from placebo.[12-14] No clinically significant difference in the incidence of adverse events was observed in patients receiving lamivudine plus IFNα, in comparison to IFNα alone.

For each category of body system, adverse events were more common for patients treated with IFNα than lamivudine monotherapy or placebo.[54-56] A significantly higher incidence of abnormal liver function tests was noted in patients receiving IFNα (21%) in comparison to those receiving lamivudine (11%). The nature and frequency of adverse events were similar for lamivudine-treated and placebo-treated patients, with the exception of a slightly higher incidence of abnormal liver function tests in the lamivudine group (11%) than in the placebo group (7%). This may have been due to the selection of resistant mutants or to other causes that need to be clarified.

During the 52 week treatment, the incidence of events was slightly higher for the placebo group than for the other treatment groups, suggesting that many of these events were due to the underlying disease. The most common serious adverse event was abnormal liver function tests, accounting for 18% events in placebo-treated patients and 25% events in lamivudine-treated patients during treatment. These abnormal liver functions tests occurred equally during and after treatment. All other serious adverse events were reported in 1% or less of each treatment group. No evidence of lamivudine-associated decompensated liver disease was noted.

To evaluate potential myopathy, serious adverse events associated with elevations of serum creatine phosphokinase (CPK) or muscle abnormalities were examined. Marked CPK elevations were uncommon, and the incidence of CPK elevations in the lamivudine cohort was not significantly different from the placebo cohort. To evaluate potential pancreatitis, serious adverse events associated with amylase or lipase elevation were evaluated. Amylase and lipase elevations during treatment were rare and almost identical in all treatment groups. The incidence of all other laboratory abnormalities were similar among placebo and lamivudine groups. Patients receiving combination of lamivudine plus IFNα did not exhibit any increased incidence of laboratory abnormalities in comparison with patients receiving lamivudine or IFN alone. No deaths were reported in these trials.

3.2 Pregnancies

Eight pregnancies occurred in the large phase III trials.[54-56] Four occurred in patients receiving lamivudine monotherapy and one in a patient receiving lamivudine plus IFNα. These pregnancies resulted in normal live births.

3.3 ALT Exacerbation

During treatment, serum ALT elevations exceeding 3-fold baseline values occurred in similar proportions of patients receiving placebo (13%) or lamivudine (13%). ALT elevations during treatment were noted in 17% of IFNα-treated patients and 7% of lamivudine plus IFNα-treated patients but these differences were not significantly different from lamivudine monotherapy. ALT elevations during treatment were generally transient, asymptomatic, and resolved on continued treatment.[54-56] In lamivudine treated patients, 20% of patients with an ALT elevation exhibited HBeAg seroconversion, in contrast to 10% of placebo-treated patients, indicating that in these cases, ALT flare was the reflect of the anti-HBV immune response.

During up to 4 months follow-up after treatment, the incidence of ALT elevations exceeding 3-fold baseline values was 19% in patients receiving lamivudine, in contrast to 8% in those receiving placebo, 17% in those receiving lamivudine plus IFNα and 16% in those receiving IFNα alone. No increase in clinically significant post-treatment ALT exacerbation was noted in patients receiving lamivudine in comparison with the other treatment groups.

3.4 Drug-Resistant Mutants

In the large phase III trials of lamivudine therapy for 12 months, the incidence of drug resistant mutants corresponding to the selection of mutations in the YMDD motif of the viral polymerase, was 14% in the Asian study,[12] 31% the European study[14] and 32% in the American study.[13] There was no difference in ALT levels in patients with wild type polymerase sequence and those with the mutation in the YMDD motif.

After lamivudine cessation the incidence of polymerase mutants was analysed in one study which showed a decrease from 31% at the end of treatment to 21% 12 weeks later, suggesting the re-emergence of wild type virus.[14] In the Asian study there was no significant increase in ALT levels in patients with the YMDD mutant virus, nor was there a deterioration in liver histology.[12] In the US study, 43% patients with YMDD mutation presented an histological response compared with 63% patients with wild type sequence[13] (table IV). As these polymerase mutants are not cytopathogenic by themselves, as is the wild type virus, the impact of these mutants on immune-mediated liver injury needs to be carefully assessed in a longer clinical survey which may find a slow and progressive deterioration of liver histology in these patients.[24]

In one study of extended lamivudine therapy, the incidence of YMDD mutants was 14% at week 52 and 38% at week 104.[19] Median HBV DNA in these patients was lower than pre-treatment levels. The same was true for ALT levels. Interestingly,

Table IV. Incidence of polymerase mutants during lamivudine therapy (percentage of patients)

Study	Month 12	Month 24	Month 36
HBeAg-positive			
Lai et al.[12]	14		
Dienstag et al.[13]	32		
Schalm et al.[14]	31		
Liaw et al.[19]	14	38	
Leung et al.[20]			53
Lau et al.[57]			76
HBeAg-negative			
Tassopoulos et al.[16]	27		
Hadzyiannis et al.[33]		50	
Lok et al.[34]	10	56	
Lau et al.[57]			10

HBeAg = hepatitis B e antigen.

25% of these patients developed an ALT flare (>2 × the upper limit of normal), but ALT decreased in all patients who were maintained on lamivudine therapy. HBeAg seroconversion was achieved in 23% of these patients who continued lamivudine therapy, including HBV DNA loss and normalisation of ALT levels by week 104.[19]

In another study, 51 patients receiving an extended lamivudine monotherapy were followed for 3 years.[20] The incidence of YMDD mutants was 53% at week 156. Of these patients, 27% achieved HBeAg seroconversion following the detection of the YMDD mutants. On the other hand 56% of the patients who never presented a YMDD mutant achieved HBeAg seroconversion. Median HBV DNA and ALT levels remained below the pre-treatment values over the 3 years of treatment. Nine patients with a polymerase mutant had liver biopsy at week 156; five showed an improvement compared with baseline, two had no change and two had a deterioration.

In another study, the incidence of YMDD mutant was 76% at year 3 of treatment in HBeAg-positive patients and only 10% at year 2.5 of therapy in HBeAg-negative patients.[57] This was confirmed in an independent study that showed that the rapidity of selection of YMDD mutant during therapy depends on pre-treatment ALT and HBV DNA levels as well as on the pre-core sequence status.[58] Furthermore, lamivudine withdrawal led to the re-emergence of wild type sequence but retreatment led to a more rapid reappearance of the drug resistant mutant, as this was previously shown with famciclovir therapy.[57-61] Furthermore, some studies showed the possibility of clinical deterioration in these patients with ALT flares,[62] that were more frequent in patients with pre-core mutant infection.[33,58] In patients with pre-core mutant infection, lamivudine resistance may be associated in approximately 50% of cases with acute exacerbation of the liver disease. In the setting of liver transplantation, 6 of 14 patients with lamivudine resistance presented a clinical deterioration of their liver functions,[44] while other case reports described the occurrence of liver failure.[63] In these patients with severe resistance, add-on therapy with adefovir, a nucleotide analogue which is active on both wild type and lamivudine resistant strains, provides a new treatment option to rescue these patients.[42,43]

The long-term effect of lamivudine resistant mutants on the clinical outcome is not yet known. Phase IV and cohort studies are clearly warranted to provide new information on this issue for a better assessment of the benefits and risks of lamivudine therapy.

3.5 Rebound of Viral Replication

Anti-HBe seroconversion is the usual primary endpoint of antiviral treatment in patients infected with wild type HBV. The rate of anti-HBe seroconversion that is reported in lamivudine trials is related to on-treatment response,[12,13] while the rate of IFNα-induced seroconversion is usually reported 6 months post-treatment.[5] However, careful analysis of the published data show that HBeAg seroconversion after lamivudine therapy is usually durable in the large phase III trials that enrolled

Caucasian and Asian patients with chronic HBV infection.[12-14] Importantly, results of an Asian study showed that HBeAg seroconversion is not durable in endemic areas of HBV infection as Korea,[64] with anti-HBe loss in 37.5% and 49.2% at 1 year and 2 years of follow-up, respectively, and reappearance of HBeAg in 81% and elevation of serum ALT in 94% of these relapsers. However, in this Korean study, lamivudine was discontinued 2 to 4 months after HBeAg disappearance. As the duration of additional lamivudine therapy after HBeAg seroconversion was one independent predictive factor for post-treatment relapse, it is therefore suggested to maintain antiviral treatment for at least 6 months after anti-HBe seroconversion.[6] Moreover, few studies showed that the risk of relapse after anti-HBe seroconversion is minimal when both serum HBV DNA level decreases below 10^4 copies/ml and no pre-core mutant is selected, suggesting that monitoring of antiviral therapy should rely on quantitative and sensitive assays for HBV DNA detection and mutant detection assays.[8,17,58]

In patients with pre-core mutant infection, this specific issue is even more crucial as the endpoint of anti-HBe seroconversion is not valid in this situation. Only recent studies showed the long-term benefit of interferon alfa therapy, and the optimal duration of lamivudine therapy is clearly not known; trials are ongoing to answer this specific issue.

4. Conclusion

Lamivudine therapy is indicated in patients with biochemical and histological evidence of chronic active hepatitis with either high necroinflammatory or fibrosis indices (excluding minimal hepatitis), and viral replication (i.e. presence of circulating HBV DNA) [figures 1 and 2]. All the clinical studies have demonstrated the initial antiviral efficacy of lamivudine. As the drug has only been approved recently, the long-term clinical benefit of lamivudine treatment still needs to be determined.[6] In patients with HBeAg-positive chronic hepatitis, lamivudine administration should be continued until full serological evidence of anti-HBe seroconversion. In this case, it is associated with ALT normalisation and improvement of liver histology. The exact time to stop lamivudine after anti-HBe seroconversion remains to be determined but usual clinical practice recommends to confirm the serological results and wait for 6 months prior to treatment cessation.[6] The durability of anti-HBe seroconversion is usually high (75 to 80%), but specific studies are required to analyse the long-term outcome in these patients with lamivudine-induced anti-HBe seroconversion. However, clinicians have to face the current dilemma with lamivudine therapy: treat for a long period of time to avoid post-treatment rebound and flares, versus a short period of time to avoid the emergence of resistance.[6,24] This critical issue needs to be solved by further clinical trials and cohort studies.

In patients with HBeAg-negative chronic HBV infection (i.e., infected with pre-core mutants), the

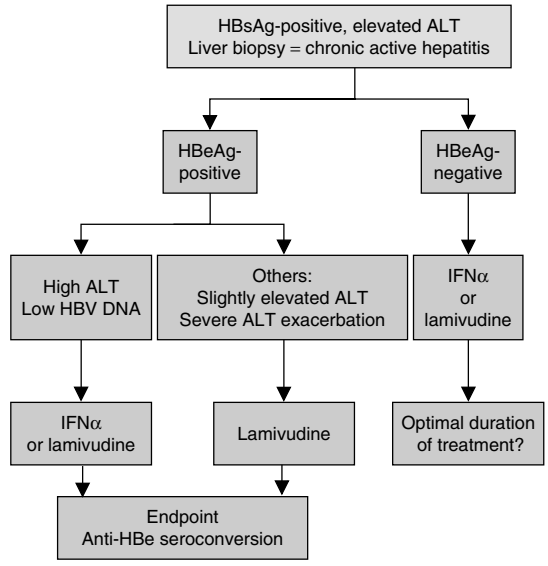

Fig. 1. Indication of antiviral treatment in patients with chronic hepatitis B virus (HBV) infection: patients with elevated ALT levels. **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **IFN**α = interferon-α.

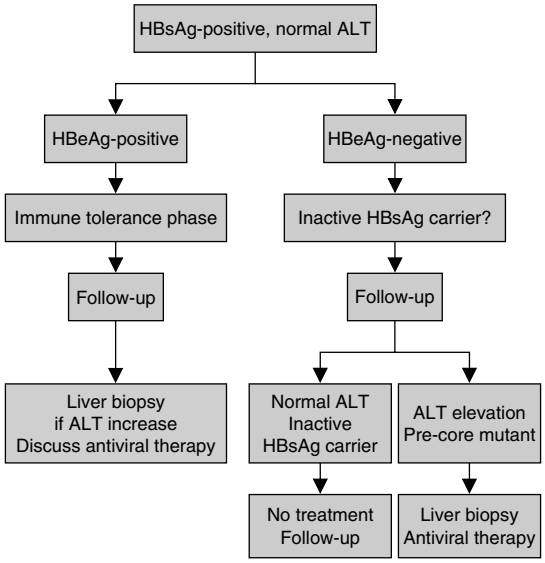

Fig. 2. Indication of antiviral treatment in patients with chronic hepatitis B virus infection: patients with normal ALT levels. **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen.

frequency of relapse is high and the optimal duration of lamivudine therapy is not known. Specific studies are warranted to define the best therapeutic regimen in these patients.

In patients with liver cirrhosis, lamivudine administration may improve the clinical status of patients dramatically. However, drug resistance may then appear and this may make the decision as to whether to proceed to liver transplantation difficult. In these patients, the decision to start lamivudine therapy should be discussed with the liver transplantation team mainly depending on the expected time on the waiting list. In transplanted patients, the most recent studies indicate that the best prophylactic strategy relies on the combination of HBIG and lamivudine. However, in the view of reducing the cost of liver transplantation, studies are ongoing to determine what is the best prophylactic regimen, especially in terms of protocol duration. Currently, lamivudine administration is the only antiviral drug available to treat HBV infection in patients with organ transplantation.

Finally, the most serious adverse event that have to be taken into account are the ALT exacerbation related to early treatment cessation, or to the selection of drug resistant mutants harbouring mutations in the catalytic site of the viral polymerase. New inhibitors of HBV replication that are almost as potent on wild type HBV as on lamivudine resistant strains, such as adefovir, are being developed and should provide new rescue options as well as the possibility of *de novo* multiple drug therapy.

Phase IV and cohort studies to determine, in the setting of routine clinical practice, the efficacy of lamivudine and the factors associated with virological response and viral resistance are still warranted.

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Correspondence and offprints: Dr *Fabien Zoulim*, INSERM Unit 271, 151 Cours Albert Thomas, Lyon, 69003, France.
E-mail: zoulim@lyon151.inserm.fr