

# Treatment of HBeAg-negative chronic hepatitis B with Lamivudine

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## Summary

Although Lamivudine (LAM) is not capable of eradicating HBeAg-negative Hepatitis B Virus (HBV) infection, it can be effective in the treatment of HBeAg-negative chronic hepatitis B (CHB) as in this setting it may suppress viral replication leading to normalization of the liver biochemistry and improvement of liver histology. However, extended therapy is required and there is no indication as to when stop therapy. Withdrawal of LAM leads to return of replication of the original HBV and subsequent disease activity. Continued therapy with LAM is associated with the time-dependent risk of the emergence of LAM resistant strains of HBV and return of disease that may lead to severe hepatitic flares in some patients. The clinical impact of these flares is more pronounced in patients with advanced cirrhotic disease and appears therefore to depend largely on the residual hepatic reserve.

## Introduction

The advent of LAM has provided an alternative also to the therapy of HBeAg CHB; management of this disease with alpha-interferon (IFN) has been problematic because of the poor response and high relapse rate of short-term therapies and because of the important side effects associated with the prolonged IFN therapy required to control disease.

## Initial studies

Initial published reports of the treatment of HBeAg-negative CHB with LAM include approximately 1200 patients (1). Most were enrolled in uncontrolled open label studies with small number of patients; in some no distinction was made between HBeAg negative and positive subjects and in a few LAM was given in association with IFN. Response while on treatment was reported either as complete (HBV-DNA loss combined with alanine- aminotransferase (ALT) normalisation) or as separate biochemical and virologic responses. The histological response was also evaluated in same studies. Study end-points have varied from the maintenance of a complete response at the end of the treatment follow-up, to single time-point assessments of the virologic or biochemical parameters; the duration of follow-up has ranged from 4 to 24 months.

Overall a complete response was observed in 71% to 96% of the patients treated for 6 to 12 months and separate virologic or biochemical responses were observed, respectively, in 65% to 90% and 60% to 96% of the treated patients. Two studies comparing HBeAg-negative to positive patients (2-3) showed that the interim complete response while on therapy was distinctly better in the HBeAg-negative than positive subjects (79% vs 28.5% and 75% vs 45%), while in another study (4) response was higher in the HBeAg-positive group (73.3% compared to 62.8% in the negative group).

In the one randomized, placebo controlled, double blind international multicenter study reported by Tassopoulos (5), after 24 weeks of therapy 63% of the patients treated with LAM 100 mg/day exhibited a complete response, compared to 6% of the placebo group. By week 52 of treatment, histology improved (= 2 points reduction in Knodell necroinflammatory score) in 60% of the patients, remained unchanged in 29%

and worsened (>1 point increase) in 12%. Similar results were reported by Santantonio and coworkers in Southern Italy (6). A histological improvement after 52 weeks of LAM was reported also by Scotto in 20% (7) and by Suzuki in 95% (8) of mixed series including HBeAg-positive and negative patients; improvement, however, was independent of the presence of the HBeAg antigen.

Despite the promising results while on therapy, the relapse rate has been very high post-therapy. In the three studies (5-6,9) which evaluated sustained responses defined as complete virologic and biochemical responses that were maintained post-therapy, only 11%, 20% and 13% of the on-treatment responders maintained the response 24 months post-therapy. None of the treated patients lost the HBsAg.

These early studies showed that although LAM had significant antiviral properties which resulted in biochemical and histological control of the liver disease while on therapy in a consistent proportion of patients, treatment was not capable of eradicating the infection and viremia with associated disease relapsed on suspension of therapy.

Though the overall results were not different from those obtained with IFN therapy, a major advantage of LAM over IFN was safety and tolerability. All studies have shown that the proportion of patients with adverse events was similar in the LAM and placebo group. Minor non-specific symptoms reported during therapy were fatigue, headache, abdominal pain and pruritus; laboratory abnormalities have included transient asymptomatic elevations of serum lactate dehydrogenase (up to 40% of the patients), creatinine phosphokinase (up to 16%) and amylase (up to 16%).

### **Long-term therapy**

The conclusion that one year of LAM is insufficient to generate a sustained response off-treatment and that prolonged LAM therapy is required for suppression of viral replication and control of disease, has prompted the design of long-term studies and has led Scientific and Health Authorities to recommend the continued administration of LAM. However, LAM therapy of HBeAg-negative CHB is aggravated by the emergence of mutants that have changes in the YMDD locus of HBV-DNA polymerase, in the same fashion as with the treatment of HBeAg-positive patients (10-11); in the initial studies the incidence of YMDD mutants had varied from 15% to 27% at 12 months, increasing to 57% -64% by 24 months of therapy (5-6).

Therefore, relevant to the issue of long-term therapy of HBeAg CHB with LAM is the incidence over time of YMDD mutants and the clinical impact of their emergence. Data on these issues are becoming available from three sources:

1. A Glaxo-sponsored multinational ongoing follow-on study
2. Spontaneous studies from clinical centers
3. The generalized use of LAM in primary care on the territory.

1. In a Glaxo-sponsored study of extended LAM therapy (12-13), 76 HBeAg-negative patients with CHB were enrolled to receive 100 mg LAM daily on a 5 years follow-on study. The incidence of YMDD increased to 39% at month 12, 54% at month 24 and 57% at month 36; correspondingly, the response declined from 67% at 6 months, to 51%, 34% and 29% after, respectively, 12, 24 and 36 months. The median values of serum HBV-DNA and ALT for patients who developed YMDD variants and patients who did not develop mutants are reported in figure 1; an increase of HBV-DNA and ALT was apparent in the former.

A complete analysis at month 24 of follow-up is available (Rizzetto et al, manuscript in preparation). Among the patients who did not develop YMDD variants 72% had normal ALT and negative HBV-DNA at 24 months while only 5% of patients who developed YMDD mutants maintained normal ALT after 1 year of YMDD duration. No major clinical events, in particular no liver decompensation, occurred in patients who developed mutants.

2. One hundred and thirty HBeAg-negative patients treated at medical centers in Athens, Bologna and Turin have been followed on throughout two to three years of therapy. Most were non-cirrhotic CHB; a minority had

also compensated cirrhosis.

In the study by Hadziyiannis in Athens (14), the virologic response diminished from 68% at months 12 to 41.6% at month 30; correspondingly the rate of ALT response diminished from 96% at 12 months to 42.5% at 30 months. In a study by Lok (15), the virologic response diminished from 65% at months 12 to 60% at month 24 to 0% at month 30. In a study by Paganin (16), the rate of virologic breakthroughs increased from 8.8% at month 12 to 24.6% at month 27, but 81% of patients were maintaining a biochemical response at month 18 of treatment. In an additional study by Buti (17), 11 of 16 patients (69%) maintained a full response after two years of therapy; YMDD variants were detected in 44% of the patients at two years.

Overall the cumulative data show that approximately 30% of patients had a virologic response at 30th month of therapy and 60% maintained a biochemical response (Fig.2 and Fig.3), indicating that in about 30% of patients the emergence of YMDD mutants had not been accompanied by liver damage in the interim of the follow-up. However, among 32 patients who developed a virologic breakthrough in Greece and were further followed up for 2 years, the biochemical remission was not sustained as all developed abnormal liver enzymes by the 24 months duration with YMDD (18). The development of the biochemical breakthrough was associated with a significant increase of HBV-DNA in serum and by ALT peaks within 3 months; ALT remained persistently abnormal with fluctuation levels thereafter.

The clinical impact of virologic relapses has been minimal in 5 studies (6,13,16,17,19); liver decompensation occurred in none of the patients. It was instead significant in the study of Hadziyiannis (14); upon the emergence of YMDD mutants ALT increased to levels higher than baseline in 8 of the 17 (47%) patients who developed a virologic breakthrough and reached acute hepatitis levels in six, one of them developing jaundice.

3. With the generalized extended use of LAM in Italy, there were recent reports from the territory of severe hepatic attacks connected with the long-term use of the drug. This has prompted a national survey, promoted by the Italian Association for the Study of the Liver, to assess the magnitude and reasons of the problem.

The preliminary data from the analysis (in progress) of the clinical records of 591 HBeAg-negative patients divided in 331 chronic hepatitis, 184 Child A cirrhosis and 76 Child C cirrhosis, treated for a mean of 24.7 months, has shown that:

- ◆ A virologic breakthrough (associated with YMDD detection in 98.6% of the analysed cases) developed in 198 of the 558 responders to therapy (35.5%) after a mean time of 19.6 months from the LAM start. The frequency of virologic breakthrough was not different in the three subgroups of patients.
- ◆ LAM was stopped in 80 patients (13.5%); in 43 patients the drug was stopped after the selection of YMDD mutants, in 9 subjects because of the absence of a virologic response and in 28 for a virologic breakthrough with no evidence of YMDD selection after an initial complete response. Overall, 142 major clinical adverse events were reported in 106 patients at the emergence of YMDD mutants or after stopping LAM because of the emergence of YMDD mutants (ALT >10 the upper normal value, hepatocellular carcinoma, hepatic decompensation, liver transplantation, death). They were reported in 6,3% of non-cirrhotic CHB, in 22.8% of Child A cirrhosis and in 56.5% of Child C cirrhosis.

These results suggest that hepatic decompensation related to LAM therapy has so far occurred primarily in patients with baseline cirrhosis. Of note, previous data from patients with decompensated HBV cirrhosis, including HBeAg positive and negative cases (21-24), have reported significant clinical improvements (decrease by >2 points of the Child-Pugh score, table 1) in 33% to 66% of the patients without major complications, independent of the presence or absence of the HBeAg; however, in these studies duration of treatment has been usually limited, most of the patients ultimately undergoing liver transplantation.

## Conclusions

Data from long term follow-on LAM monotherapy studies in well-compensated HBeAg-negative CHB including predominantly non-cirrhotic disease, indicate that approximately 30% of these patients maintain a full virologic and biochemical response after 3 years of therapy. In a minority of patients disease relapse is presumably related to the reactivation of the original HBV initially inhibited by LAM. In those who develop YMDD mutants, disease may not resume immediately but will inevitably resume within 24 months. In these patients the course of recurrent disease during interim 12 to 24 months follow-up after the virologic breakthrough has been generally mild and not worse than expected in the natural history of the disease.

In contrast to these favourable results, following the generalized extended use of LAM, reports are increasing from the territory of patients who experience important hepatic flares and liver decompensation related either to the emergence of YMDD mutants during therapy or to the reactivation of the original HBV after LAM withdrawal<sup>25</sup>. Preliminary data from a nationwide survey in Italy would indicate that major adverse reactions occur predominantly in cirrhotic patients and only occasionally in non-cirrhotic disease; though the risk is distinctly higher in advanced Child C cirrhosis, it seems to be also elevated in patients with apparently compensated Child A cirrhosis.

Therefore, extended LAM therapy

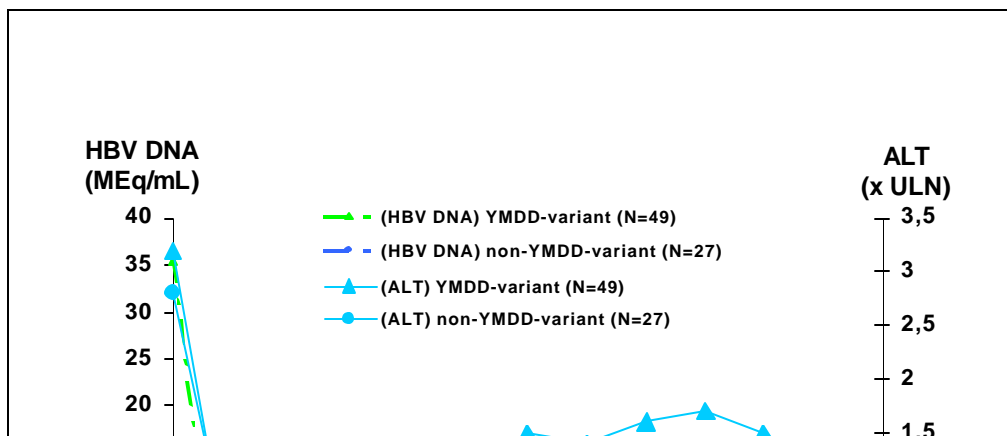
- ◆ should not be given to mild or moderate CHB with a good prognosis; the risk of developing YMDD mutants is high with extended therapy and the advantage of controlling HBV replication and disease in the short while may be offset by the clinical uncertainties associated with the long-term duration of YMDD mutants.
- ◆ is indicated in patients who have evidence of progressive (over a few years) and/or severe CHB, whose prognosis is poor and in whom the benefits of LAM therapy outweigh the risks of the emergence of YMDD.

The role of LAM therapy in HBeAg-negative CHB evolved to cirrhosis remains uncertain; the discrepant results obtained so far in uncontrolled studies may depend from different selection criteria and the clinical heterogeneity of “compensated” cirrhosis. Marginal survival advantages have been reported only for patients with decompensated HBV cirrhosis candidating to liver transplantation treated over the short-term.

Studies of the combination therapies of LAM with other antivirals are in progress in patients with HBeAg-negative CHB; a 12 month course of the combination of LAM with IFN has prevented the emergence of YMDD mutants during the treatment period, but the results after therapy suspension have been similar to LAM monotherapy (26-27).

Recent data demonstrating that Adefovir-Dipivoxil (10 mg once daily) effectively inhibits replication of YMDD mutants resistant to LAM and hence averts the resultant disease (28), suggest that this drug may be used as rescue therapy in this setting.

**Fig. 1 - Median ALT and HBV DNA in patients with and without YMDD variant HBV**  
UNL = Upper Normal Limit



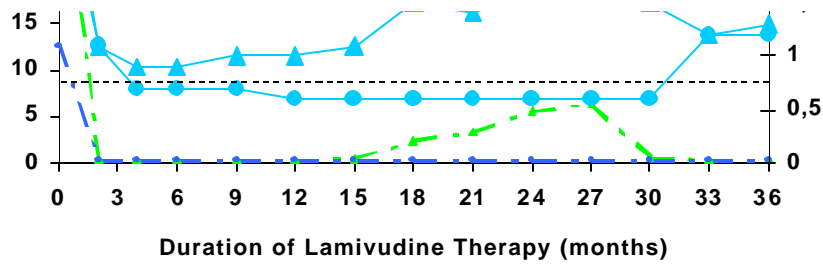


Fig. 2 - Extended Lamivudine therapy in HBeAg neg CHB; mean virological remission

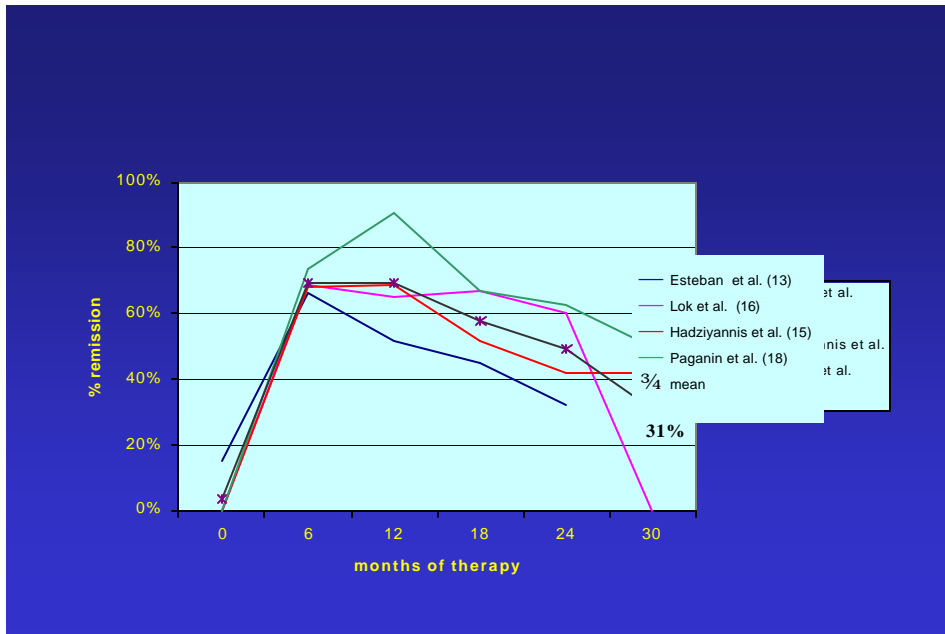
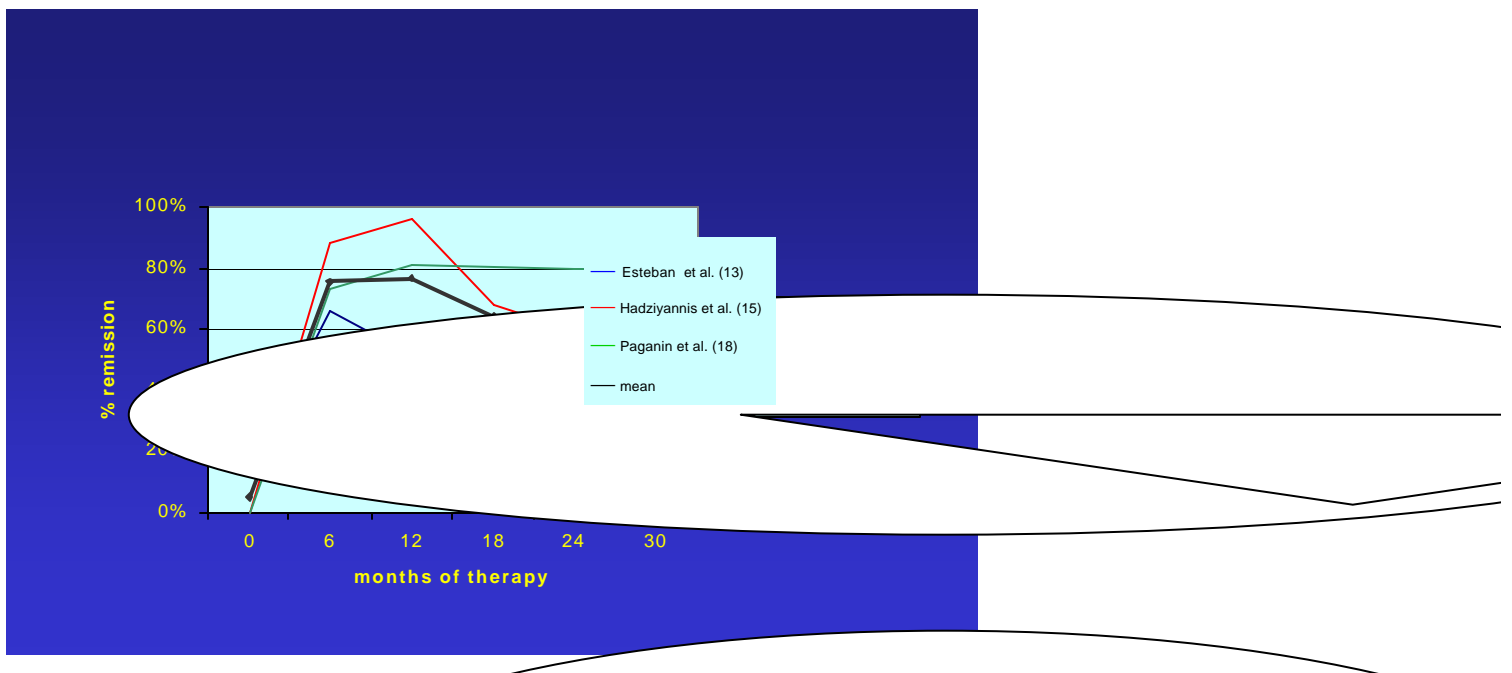


Fig. 3 - Extended Lamivudine therapy in HBeAg neg CHB; mean biochemical remission



**Table 1. Clinical improvement :**

Reference				by $\geq$ 2 points of Child Pugh score
Villeneuve, 2000				66%
Kapoor, 2000				50%
Lampertico, 2000	44			
Yao, 2001	23	13		61%
Marzano, 2001	33	5-6	73	33%

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