

## Lamivudine for Chronic Hepatitis B

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Lamivudine, the negative enantiomer of 3' thiacytidine, was the first oral agent approved for therapy of chronic hepatitis B and revolutionized the management of the disease. In addition to its usefulness in patients with interferon-responsive profiles, it is effective in difficult to treat populations such as those with high levels of HBV DNA, decompensated cirrhosis, and post-liver transplantation. The initial randomized, placebo controlled studies demonstrated the clinical benefit and safety of lamivudine in both hepatitis B e antigen (HBeAg) positive and negative chronic hepatitis B, in populations who acquired their infection during infancy/childhood and during adulthood.

The primary endpoint of trials in HBeAg-positive chronic hepatitis B was improvement in liver histology, defined as a decrease in necroinflammation by  $\geq 2$  points using the Knodell histology activity index (HAI); this was achieved in 52-56% of lamivudine-treated subjects compared to 24% in placebo-treated controls. Secondary endpoints of HBeAg loss and seroconversion (HBeAg loss and gain of anti-HBe), virologic response defined as complete suppression of HBV DNA below the level of detection using the less sensitive liquid hybridization assay (cut-off of 1.6 pg per/ml), and a biochemical response defined as normalization of serum ALT level were achieved more frequently in lamivudine-treated patients compared to controls. HBeAg seroconversion was observed in 16-18% of patients compared to 4-6% of controls. Almost all patients (85-98%) achieved an on-treatment viral response; however, this declined to 62-72% at end of treatment due to the progressive emergence of viral resistance and viral rebound. Of patients with elevated ALT at baseline, normalization was seen in 41-72% of lamivudine recipients compared to 7-24% of placebo controls. The virologic relapse rate after a year of therapy was high in the absence of an HBeAg seroconversion, although median HBV DNA levels were lower compared to baseline. The incidence of genotypic resistance defined as the presence of the YMDD mutation on the HBV polymerase was approximately 25% of sampled cases (range 14-32%). Genotypic resistance was almost always associated with virologic breakthrough and reappearance of HBV DNA in serum. Rates of HBsAg loss were less than 1%.

Recent studies using lamivudine as the benchmark for assessing efficacy and safety of newer agents have provided updated virologic information on the efficacy of lamivudine using more sensitive PCR-based assays. Using the more sensitive PCR-based assays, end-of-treatment viral clearance, defined as HBV DNA levels below 300-400 copies per ml, were achieved in 36-40% of patients compared to 62-65% using the less sensitive bDNA and AxSym assays (cut-off .7 MEq/ml and  $10^5$  copies/per ml, respectively). The median decline in HBV DNA was 5.6 to 5.8 log copies/ml. Histological response, rates of HBeAg seroconversion, and biochemical response were similar to previously reported trials (see Table 1.) Interestingly, normalization of ALT level at end of therapy more

closely mirrored the virologic response when measured by the less sensitive assays, suggesting that complete virologic suppression is not a *sine qua non* for a biochemical response. Nevertheless, the goal of treatment should be to achieve HBV DNA negativity by PCR. The single best predictor of HBeAg seroconversion was a high baseline serum ALT. Other predictors included low pre-treatment HBV DNA level, younger age, and genotype B compared to C.

Durability of HBeAg seroconversion after lamivudine withdrawal has been an uncertain issue. Early studies suggested that the relapse rate after HBeAg seroconversion defined as reappearance of HBeAg in serum was low: 14% and 28% at 1 and 2 years off therapy, respectively. However, later studies reported higher rates of HBeAg reversion. Cumulative rates of HBeAg relapse were 38-42% at 1 year, 49% at 2 years and 54% at 3 years; notably, more than 50% of patients relapse within the first 24 weeks after therapy is stopped. Nonetheless, despite these different results, the durability of HBeAg loss appears to be lower than that reported with interferon. Predictors of relapse include low baseline serum ALT, high pre-treatment HBV DNA, male sex, and the duration of lamivudine therapy after HBeAg loss. Race and genotype were not found to influence relapse.

Long-term therapy has been explored because of the low rate of HBeAg loss and the high relapse rate after 1 year of therapy. Continuing therapy beyond a year was associated with an increased rate of HBeAg seroconversion and further histologic improvement. Cumulative rates of HBeAg seroconversion increased from 18% to 29% to 40% to 47% at 1, 2, 3, and 4 years, respectively. Additionally, histologic improvement was either maintained or continued to increase with extended therapy. At 3 years 60% of patients remained stable and 19% continued to improve. Importantly, 75% of patients with cirrhosis improved. Minimal progression was noted. Unfortunately, enthusiasm for these very encouraging results had to be tempered due to a concomitant increase in the rate of virologic resistance from 25% at 1 year to 74% at 5 years; the development of resistance abrogated most of the clinical benefit of extended therapy. In addition to the loss of virologic and biochemical responses, patients with virologic resistance had less histologic improvement and were more likely to deteriorate compared to those without resistance.

Lamivudine has also been shown to be effective for HBeAg-negative chronic hepatitis B. In a double-blind placebo-controlled trial, 63% of lamivudine-treated patients achieved a combined virologic and biochemical endpoint as previously defined at week 24, compared to 6% of patients receiving placebo. However, as with HBeAg-positive patients, this initial beneficial response was eroded by the development of viral resistance, and virologic response declined from 65% at year 1 to 52% and 42% at years 2 and 3, respectively. Biochemical responses decreased concomitantly with the virologic response, from 90% at year 1 to 63% at year 2, and 53% at year 3.

Recent studies using the more sensitive virologic assays have also been conducted in HBeAg-negative cohorts. A significantly higher proportion of HBeAg-negative patients achieved a complete virologic response by PCR assays (cut-off < 300-400 copies/ml) 72-73% as well as normalization of serum ALT level, 71-73% compared to HBeAg-positive

patients (probably due to lower baseline HBV DNA levels) (see Table 1). Rates of histologic improvement were similar to HBeAg-positive patients, but rates of virologic resistance appeared to be lower both in the short- and long-term. Relapse rates after 1 year of therapy were extremely high, with 90% of patients experiencing virologic relapse. These studies suggest that short-term therapy is inadequate to achieve long-term remission, and long-term therapy seems to be mandatory for this group of patients. However, a sustained virological response of 50% was reported in patients treated for 2 years. Long-term therapy (4-5 years) has been associated with increased patient survival and event-free survival.

Lamivudine has an impressive safety record, and side effects are generally no different compared to placebo. It has also been used safely in pregnancy. A major safety issue with lamivudine therapy is ALT flares due to the emergence of viral resistance and following withdrawal of lamivudine. These occur at a rate of 10-15% and 5-10%, respectively. Hepatic decompensation and death have been reported to occur as a result of these flares.

Although lamivudine is approved for use as a first-line agent for both HBeAg-positive and negative chronic hepatitis B, its efficacy is severely limited by viral resistance, especially in the case of HBeAg-positive chronic hepatitis B. In the era of newer antiviral agents, its role should be re-assessed as the development of lamivudine resistance can have a negative impact on future therapy (for example, resistance to entecavir has only been reported in the setting of lamivudine resistance).

Thus, only HBeAg-positive patients who have a favorable response profile should be offered therapy with lamivudine unless contraindications to other agents exist. HBeAg seroconversion is a reasonable end-point for stopping therapy, but patients should continue lamivudine for a minimum period of 4-6 months before discontinuing lamivudine, and they should be monitored closely for relapse and the development of withdrawal flares. Viral breakthrough due to the development of resistance should trigger rapid initiation of a second agent effective against the lamivudine-resistant virus to prevent loss of clinical response or clinical deterioration. Lamivudine might still have a role to play in management of HBeAg-negative chronic hepatitis B. Therapy should be continued indefinitely until either one of two endpoints occurs: either loss of HBsAg or the development of resistance. Although lamivudine has an excellent long-term safety profile and is the cheapest of the oral agents, it may be near the end of its run as a first-line agent. It will still have a niche in special situations where short-term use is required, as in prevention of HBV reactivation during chemotherapy, during pregnancy, to prevent decompensation during acute infection, and finally in combination with other agents where theoretically the chance for resistance is lowered.

Table 1: Recent studies using lamivudine as a comparator drug in HBeAg-positive and negative chronic hepatitis B.

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<b>HBeAg positive</b>	<b>HBeAg negative</b>
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Reference	Lau 2005	Chang 2006	Marcellin 2005	Lai 2006		
<b>Number of subjects</b>	272	272	355	181	181	313
<b>Timepoint</b>	Week 48 (ETR)	Week 72 (SR)	Week 48 (ETR)	Week 48 (ETR)	Week 72 (SR)	Week 48 (ETR)
<b>Response</b>						
<b>Biochemical</b>						
Normal ALT (%)	168 (62)	76 (28)	213 (60)	132 (73)	80 (44)	222 (71)
<b>Virologic</b>						
HBV DNA (-) PCR (%)	108 (40)	14 (5)	129 (36)	133 (73)	12 (7)	225 (72)
HBV DNA (-) Hybridization (%)	169 (62)	60 (22)	232 (65)	154 (85)	53 (29)	279 (89)
Mean log copies/ml (%)	-5.8	-1.9	-5.4	-4.2	-1.6	-4.5
HBeAg loss (%)	59 (22)	57 (21)	70 (20)			
HBeAg seroconversion (%)	55 (20)	52 (19)	64 (18)			
HBsAg loss (%)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)
Resistance (%)	69/254 (27)		45 (13)	32 (18)		23 (7)
<b>Histologic</b>						
HAI decrease $\geq 2$ points (%)		93 (51)	195 (62)		72 (58)	174 (61)
<b>Combined Response</b>						
HBeAg seroconversion/ HBV neg. (Hybridization) (%)	50 (18)	28 (10)	67 (19)	125 (69)	42 (23)	

ETR End-of-treatment response

SR Sustained response 24 weeks after stopping therapy

## References

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