Treatment with lamivudine for non-immunocompromized patients with chronic hepatitis B

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Hepatitis B virus (HBV) infection remains a considerable health problem worldwide and a significant cause of liver disease and liver cancer in humans. The objective of treatment of chronic hepatitis B (CHB) is to suppress HBV replication to prevent progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Interferon alfa (IFN-α) is currently the most effective and the only approved treatment for CHB. However, the relative rate of hepatitis Be antigen (HBeAg) disappearance induced by IFN-α in unselected patients ranges from 20% to 30%. Lamivudine, the negative enantiomer of 2'3'-dideoxy-3'-thiacytidine, is an oral nucleoside analogue that inhibits viral DNA synthesis by terminating the nascent proviral DNA chain. Unlike some dideoxynucleosides, lamivudine does not inhibit mitochondrial DNA synthesis or the proliferation of cells at concentrations that block the synthesis of viral DNA and does not include mitochondrial toxicity *in vitro*. The compound has been well tolerated in long-term studies of patients with human immunodeficiency virus (HIV) infections at doses of 600 mg/day for more than 1 year. *In vitro* and *in vivo* models of HBV infection showed that lamivudine potently inhibited HBV replication.

In the 3 clinical trial published until now, lamivudine therapy induced rapid decreases in serum HBV DNA concentration in all patients irrespective of the baseline HBV DNA concentration. Undetectable serum HBV DNA, measured by liquid hybridization assay, is already attained by week 2 in more than 50% of the patients. Less then 10% of the patients do not experience total suppression of serum HBV DNA at the end of the treatment period. In the reduction in serum HBV DNA concentration daily 100- and 300- mg doses are superior to the 25- mg dose. The 300- mg dose provides no advantage in antiviral effect (loss of HBV-DNA as assessed by the liquid hybridization assay) ; however on the level of PCR more patients reach the level of undetectability with the 300- mg dose in comparison to the 100- mg dose. Of the patients with abnormal transaminases at baseline more than 50% of them have normal ALT by the end of a 6 month treatment periode and half of the patients have histological improvement at the end of a 1 year treatment period. Unlike IFN-α, the response to treatment of lamivudine is not dependent on pretreatment characteristics and as such the drug is also effective in patients with normal transaminases, high level of HBV DNA, patients from Asian origin and in previous IFN-α non-responders. Despite the potent suppression of replication observed with lamivudine sustained response to therapy (up to 12 months) is achieved in only 20% of the patients. Considerably longer-term treatment regimens may be required to induce a better sustained response. Lamivudine is well tolerated. Serious side effects have been observed only in about 5% of patients ; they include anemia, neutropenia, nausea and neuropathy. Increased lipases may occur, but uncommonly, and serious lactic acidosis has not been observed. Twenty % of the patients show a marked increase in serum HBV DNA after treatment with a subsequent elevation of ALT 8-20 weeks after treatment. In most patients, the acute hepatitis-like events are asymptomatic and can be related to the return of HBV replication after treatment cessation. In 2-4% of the patients a clinically significant post treatment disease flare is observed. Careful monitoring remains indicated if lamivudine therapy is withdrawn in patients with marginally compensated liver disease, because severe reactivation of HBV replication may induce decompensation. On the other hand spectacular improvement of the general condition have been observed in several patients with a decompensated cirrhosis treated with lamivudine awaiting livertransplantation. In these cases therapy should not been interrupted even after seroconversion. "In treatment" ALT abnormalities have also been reported in some of the Western patients, but in all of them this was of no clinical significance.

Resistance to lamivudine based on treatment-emergent mutations in the HBV polymerase gene, has been observed in around 15% of the patients ("breakthroughs"). In all of the studied cases to date involving compensated chronic hepatitis B patients, HBV DNA breakthrough was observed only after periods of lamivudine treatment of 6-12 months or more.

In summary, lamivudine potently suppresses hepatitis B replication in chronic hepatitis B patients irrespectively of viral level or race and leads to a reduction in inflammatory activity. This is associated with improvement of liver impairment in decompensated patients. Sustained seroconversion is obtained in 20% of the patients. In patients with decompensated cirrhosis interruption of treatment can cause a lethal flare up of disease activity. The current data support investigation of longer treatment durations.

References

1. DIENSTAG J.L., PERRILLO R.P., SCHIFF E.R., BARTHOLOMEW M., VICARY C., RUBIN M. A preliminary trial of lamivudine for chronic hepatitis B infection. *The New Engl. J. Med.*, 1995, **333** : 1657-1661.
2. LAI C.L., CHING C.K., TUNG A.K., LI E., YOUNG J., HILL A., WONG B.C., DENT J., WU P.C. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers : a placebo-controlled trial. *Hepatology*, 1997, **25** : 241-244.
3. NEVENS F., MAIN J., HONKOOP P., TYRRELL D.L., BARBER J., SULLIVAN M.T., FEVERY J., DE MAN R.A., THOMAS H.C. Lamivudine therapy for chronic hepatitis B : A six-month randomized dose-ranging study. *Gastroenterology*, 1997, **113** : 1258-1263.