Treatment of chronic hepatitis B : Lamivudine

N. Leung

Prince of Wales Hospital, Hong Kong, China.

Lamivudine is the negative enantionmer of 2'-deoxy-3'- thiacytidine. It is an oral cytidine analogue with potent inhibitory effects on hepatitis B viral DNA polymerase and the reverse transcriptase. Its therapeutic efficacy has been assessed in viraemic patients, both those with positive HBeAg (wild type) and negative HBeAg (presumed precore mutant), in a number of large-scale phase III clinical trials worldwide. These trials were randomized placebo or active controlled, comparing lamivudine to placebo, standard interferon or lamivudine-interferon combination. 16-18% HBeAg positive patients seroconverted by the end of one year therapy with lamivudine 100mg daily. Pre-treatment serum ALT level has important impact on seroconversion rate : < 2 X ULN 5- 11 %, 2-5 X ULN 15-23% and > 5 X ULN 38-80%. Other baseline characteristics such as age, gender, ethnicity, previous interferon treatment, presence of fibrosis or cirrhosis, or HBV-DNA level do not influence seroconversion rate. Durability of HBeAg seroconversion off treatment is around 80%. There is incremental increase in seroconversion rate with extended therapy. In the 58 patients randomised to continuous lamivudine 100 mg daily continuously for three years in the Asian study, the seroconversion rate for patients with baseline ALT > 2 X ULN were 38%, 42% and 65% by the end of one, two and three year therapy. Among HBeAg negative patients on lamivudine 100 mg daily for 24 weeks, 63% had complete response with undetectable HBV-DNA and ALT normalization compared to 6% in the placebo group. Complete response was maintained with continued treatment up to week 52. There were 5 (9%) nonresponders to lamivudine treatment, with lower but measurable serum viral level.

The effect of one year therapy on liver histology was assessed by in a blinded manner by central pathologists using Knodell and Ishak histologic activity index (HAI) scoring system and ranked assessment. 50-70% of patients in all trials had ≥ 2 points improvement in necroinflammation. Furthermore, 2 placebo controlled trials showed more patients had worsening of fibrosis following placebo compared to lamivudine (15% vs 3% ; p = 0.0009 and 27% vs 6% ; p = 0.004 respectively). In the active control study with interferon-alpha, 17% of lamivudine treated patients had worsening fibrosis compared to 30% in the interferon-alpha ; p = 0.051. Progression to cirrhosis was observed in 7.1 % of placebo treated patients compared to only 1.8% of lamivudine treated patients, indicating the potential of lamivudine in reducing the mortality and morbidity associated with the complications of cirrhosis.

The safety and efficacy of lamivudine has been evaluated in patients with advanced cirrhosis in the setting of clinical studies of its therapeutic role before and after liver transplantation. Improvement in liver function has increased pretransplant survival and obviated the need for liver transplant in some patients. Lamivudine therapy before and after liver transplantation with combination of a short course of HBIG may be able to improve the long-term outcome after liver transplantation for chronic hepatitis B with cirrhosis.

The benefit of lamivudine must be balanced against the issues of emergence of drug resistant YMDD variants. Variants may start to emerge at the end of first year of treatment. The incidence increases with extended therapy, up to 50% by the end of the third year. Data so far indicate that the variants are less competent in replication. Median serum HBV-DNA and ALT level of the variants remained below the baseline levels. In the Asian study, comparison of baseline and year three liver histology was available in 82 patients. Among the 37 patients who did not have YMDD variants, 68% improved and 22% worsened. Among the 45 patients with YMDD variants, 56% improved and 36% worsened. Therefore the clinical impact of YMDD variants need to be carefully reviewed.

Lamivudine is indeed a milestone in the treatment of chronic hepatitis B. However, important issues need to be addressed :

[1] What category of chronic hepatitis B patients will best benefit from the treatment ?
[2] What is the optimal duration of treatment especially in those who fail to seroconvert ?
[3] How to manage patients with YMDD variants ?

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Correspondence : N. Leung, Prince of Wales Hospital, Department of Medicine Chinese University of Hong Kong, Shati, China.
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