Therapeutic Guidelines on Management of Chronic Hepatitis B in Asia

Dr. Nancy Leung
Department of Medicine and Therapeutics, Prince of Wales Hospital,
The Chinese University of Hong Kong

Abstract
Lamivudine marks another milestone in the history of therapy for chronic hepatitis B. It facilitates HBeAg seroconversion primarily in patients with moderately raised ALT, improves liver histology, reduces fibrosis and prevents cirrhosis. The benefit is also seen in HBeAg negative chronic hepatitis B patients. Extended therapy benefits some, but those who fail to seroconvert run the risk of developing drug resistant YMDD mutants with relapse of hepatitis. This therapeutic dilemma underscores the importance of careful consideration to balance the risk benefit of treatment. Various organisations like ASIAHEP, Asia Pacific Consensus, the National Institute of Health, USA and the Hong Kong Association for the Study of Liver Diseases concurred that viraemic patients should only be treated with lamivudine if ALT is >= 2 x ULN. Meanwhile, interferon should still be considered for non-cirrhotic patients with ALT 2-5 x ULN. The urgency to treat now has also got to be placed in the context of the rapid development of more effective new agents and their combination.

Introduction
Chronic hepatitis B (CHB) infection is a major health burden in Asia. Asians make up three quarters of the 300 million HBsAg positive individuals worldwide. They are mostly infected perinatally. Most went through life not aware of the infection until complications occur. The medical professionals mainly dealt with salvaging end-stage complications; like ascites, spontaneous bacterial peritonitis, bleeding oesophageal or gastric varices, hepatocellular carcinoma and hepatic encephalopathy. The immense impact of CHB is particularly felt when mostly middle-aged men at their most productive age are affected. However these complications make up the tip of the iceberg of CHB infection. Beneath the iceberg lies the bulk of CHB that is asymptomatic, subclinical, yet can be active and progressive.

Major advances have been made in controlling CHB. Effective hepatitis B vaccine and successful implication program is the mainstay. Plasma derived vaccine and recombinant vaccine are equally effective and safe. All Asian countries are working hard towards a universal vaccination program of all newborns. Taipei implemented their program thirteen years ago and is witnessing a falling incidence of childhood hepatocellular carcinoma. The prevalence of CHB among children was reduced markedly.

Some Asians still hold the pessimistic view that there is no effective treatment for CHB. Some resort to herbal remedy of no proven efficacy. However, effective therapy is now available and every effort must be made to identify and treat those who will benefit. Successful therapy resolves disease activity and reduces complication rate.

Natural History of CHB
Individuals infected with hepatitis B virus since birth follow diverse clinical courses. Over 90% become HBsAg positive for the rest of their life and have CHB. In childhood and early adulthood, the host is immune tolerant to the virus. The interaction between the virus and
the host immune system is important in determining the degree of hepatitis. Thus the virus level can be alarmingly high yet no inflammation occurs in the liver. Around 70% have uneventful CHB throughout their life, having eliminated most of the virus early on without liver injury. In contrast, the remaining 30% have prolonged active viral replication and necroinflammation of the liver resulting in significant liver disease. Using serum alanine aminotransferase (ALT), the wax and wane of necroinflammation can be monitored. Years of disease activity will progress to cirrhosis. Early cirrhosis can still escape notice when the liver function is intact and the structural alternations have not give rise to obvert clinical signs. Cirrhosis of Child' B and C grade is more likely to be associated with complications. Hepatocellular carcinoma also arises mainly in association with liver cirrhosis and necroinflammation. Identification and therapy to these 30% CHB patients are our immediate aim. One must emphasise that this target group of CHB has subclinical infection and chronic hepatitis without them realising it. We need strategy to educate the public and healthcare infrastructure to assess and identify those needing treatment.

Complete assessment should consist of interval blood tests including serum ALT (inflammation), total bilirubin, albumin and prothrombin time/INR (liver function), HBeAg/anti-Hbe/HBV-DNA (replicating status of HBV) and ultrasound of the abdomen (presence of cirrhosis and complications). It is important to understand the sensitivity of the HBV-DNA assay. Chiron bDNA, Digene and Amplicor can detect down to around 50,000 to 70,000 copies/ml. These assays are commercially available but costly. Polymerase chain reaction (PCR) assay is very sensitive (detecting 500 copies/ml), but technically demanding and not necessary in clinical practice. In immune tolerance phase, HBeAg is positive with high HBV-DNA and normal ALT. ALT and HBV-DNA levels fluctuate in immune clearance phase. Transformation from immune clearance to quiescent phase is heralded by HBeAg seroconversion, (HBeAg negative and anti-Hbe positive), undetectable HBV-DNA and normalisation of ALT. Patients most at risk are those with years of fluctuating ALT and HBV-DNA levels. Necro-inflammation and progressive fibrosis will result in cirrhosis in years.

While HBeAg seroconversion can be used as a serological marker of viral clearance, two exceptional scenarios have to be considered. Firstly, reversion occurs in as many as 32% of patients within 2 years of HBeAg seroconversion. Secondly, HBeAg seroconversion but detectable HBV-DNA indicates precore/core region mutation resulting in replicating virus that does not secret HBeAg. The incidence of precore mutant increases with the age of CHB. It can cause liver disease but comparative study with the wild type is not available yet.

Management and Therapy

Development in CHB therapy has gathered momentum in the last few years. Interferon is now joined by lamivudine as the mainstay in treatment. An exciting array of potentials - emtricitabine (FTC), adefovir dipivoxil, enticavir, DAPD, L-FMAU, therapeutic vaccines, thymosin, small molecules LdT, herbal medicines - are awaiting formal clinical assessment.

Interferon Monotherapy

The clinical efficacy of interferon monotherapy has been well established over ten years ago. Large scale controlled clinical trials data are lacking. The meta-analysis by Wong et al in 1994 showed clearly that interferon therapy at 3-5 MU per M² for 4-6 months resulted in significant viral suppression (37% vs 17%, p<0.001), HBeAg seroconversions (33% vs 12%, p<0.0001) and HBsAg loss (8% vs 2%, p<0.0001) compared to the control group. The impression that Asians respond less favourably is not substantiated. Better response is observed with moderately raised ALT, low HBV-DNA level, female gender, and occurrence
of ALT flare during treatment. Side effects are tolerable but must be closely monitored with 4 weekly assessment and complete blood count and liver function tests. Initial "flu"-like symptoms can be ameliorated with paracetamol. Bone marrow suppression, ALT flare, depression, hair loss, weight loss, and thyroid dysfunction sometimes necessitate dosage reduction or discontinuation. Interferon should still be an option in the treatment of non-cirrhotic HBeAg positive patients with mild to moderate disease activity. Therapy duration is well-defined and benefit in reduction of complications among the responders has been reported in long-term follow-up.

Lamivudine Monotherapy

Lamivudine, an oral nucleoside analogue with potent anti-viral action, is now available in Hong Kong. It is mainly excreted by the kidneys and dosage reduction is required when creatinine clearance falls below 50 ml/min. Lamivudine 100 mg daily reduces serum HBV DNA level by 2 to 3 log10 within 8 weeks. In 5 large-scale phase III randomised double-blinded placebo- or active-controlled trails worldwide, lamivudine has been shown to have significant reduction in viral load, ALLT normalisation and histologic improvement.

Serum HBV-DNA became undetectable within 8 weeks of lamivudine, though still PCR positive. One year of lamivudine induced HBeAg seroconversion in 16-18% of treated patients, compared to 4-6% in placebo (p<0.05) and 19% with interferon. Baseline serum ALT was soon recognised as the single most significant predictor of seroconversion: 64% (p<0.01) if ALT >= 5 x ULN, 26% (p=0.03) if ALT 2-5 x ULN, and 5% if ALT <2 x ULN. After ALT adjustment, Asian and Caucasian patients have the same HBeAg seroconversion rate, and is durable in >= 50% one year after treatment was stopped. Raised ALT at baseline gradually normalised. More importantly, one year lamivudine therapy significantly improved necroinflammation, reduced progression of fibrosis, and the histologic activity index (HAI) was reduced by >= 2 points in 62-70% of the treated patients, compared to 30-33% of the placebo group. Lamivudine reduced progression of fibrosis compared to placebo, 3% vs 15% (p<0.01) and fewer patients progressed to cirrhosis, 1.8% vs 7/1% respectively.

Extended therapy may seem a logical strategy. 58 Asian patients constituted a cohort in the Asian Study to address this issue. Incremental HBeAg seroconversion over 4 years was observed: 22, 29, 40 and 47% respectively. The selected group of 26 with baseline ALT >= 2 x ULN had better seroconversion rate: 38, 42, 65 and 73% respectively. Unfortunately, the benefit of extended therapy was offset by emergence of drug resistant virus, commonly known as the YMDD mutants. It continued to emerge at an annual rate of around 20% when therapy was continued.

The reason why YMDD mutants emerges is not hard to understand. Lamivudine suppresses but not eradicates the virus. Serum viral level may be low due to suppression of viral replication. Yet resilient cccDNA (covalently closed circle DNA) is largely unaffected in the hepatocytes. HBV variants resistant to lamivudine emerged under selection pressure, usually from the sixth month of therapy. After one year of treatment, 14-30% of the patients harbour the mutants. Extended Asian Study showed a continual trend of variants emergence. The cumulative rate is 17, 40, 55, and 67% respectively at the end of each successive year. YMDD mutant is less competent in replication when compared with the wild type and therefore the serum HBV-DNA level is generally lower than the baseline value. Continuing treatment will ensure suppression of the wild type but breakthrough viraemia at higher levels may occur with relapse of hepatitis. One of the centres of the Asian Study in Taipei showed 30 (93.7%) of the 32 patients with YMDD mutants had raised ALT. 13 (40.6%) experienced acute exacerbation after a median of 24 weeks (range 4-94 weeks) after the mutants emerged. More importantly, 3 patients suffered hepatic decompensation. They all recovered with HBeAg seroconversion. HBeAg seroconversion
does occur in the presence of YMDD mutants but at half the rate of the wild type. After 1-2 years of the harbouring mutants, histology can be worse off than the pre-treatment one. This means that active disease with the mutant had largely reversed the benefit from the first year of therapy. In the Asian Study, one death occurred from liver failure complicated by spontaneous bacterial peritonitis shortly after YMDD mutants emerged.

The long-term impact of YMDD mutants is far from certain and attempts must be made to minimise their emergence. No useful clinical predictors have been identified. The predictive factors included high body weight, body mass index, and high HBV-DNA level at baseline. Strategy should aim at achieving response within one year of therapy, thereby avoiding YMDD mutants emergence. Diagnostic assay for the YMDD mutants is not available in most centres. Viral breakthrough despite good drug compliance is almost diagnostic. Fortunately, preliminary data show effective therapy for YMDD mutants are likely to be available soon. These include nucleoside analogues adefovir and entecavir.

Combination of lamivudine with other antiviral agents or immune modulators is likely to be more effective. Lamivudine and interferon combination with or without lamivudine priming showed encouraging results in clinical trial. HBeAg seroconversion at the end of 1 year was 29% for combination, 18% for lamivudine, 19% for interferon and 4% in placebo. Combination of lamivudine and interferon deserves further assessment. Viral dynamic studies showed more rapid decline of serum HBV-DNA and eventually viral eradication in combination therapy of two different nucleoside analogues. Agents that can eliminate cccDNA in the infected hepatocyte, either by direct antiviral or indirect immune activity, is also likely to be able to achieve viral eradication early and minimise risk of drug resistance or relapse on stopping treatment. There are a number of potential candidates for the combination. Some have already data showing certain degree of efficacy, including famciclovir, thymosin, emtricitabine (FTC), adefovir dixipoxil and entecavir. New agents such as FMAU, LdT, therapeutic vaccines and herbal medicine are possibilities to be assessed.

Lamivudine for Decompensated Liver Disease

Data from clinical trials so far address lamivudine treatment for patients with compensated liver disease. On-going international trials for therapy in viraemic Child's A and B cirrhotic patients will evaluate lamivudine in the prevention of complications and reduction in mortality. Meanwhile, reports of marked improvement in transplantation candidates with decompensated liver disease are encouraging. Some patients were able to be de-listed from the liver transplantation list. For those who require liver transplantation, lamivudine also greatly reduced re-infection of the liver graft. This changed the entire outlook of transplantation for hepatitis B liver disease.

Asia Pacific Guideline on Management of Chronic Hepatitis B

Indication for Therapy
ALT >2 x ULN and HBV-DNA positive one month apart
*No therapy if ALT <2 x ULN
*Pre-treatment liver biopsy recommended

Choice of Therapy
ALT 2-5 x ULN: Lamivudine 100 mg daily or Interferon 5 MU three time weekly
ALT >= 5 x ULN: Lamivudine 100 mg daily

Duration of Therapy
Interferon: 6 months
Lamivudine: Stop 3 months after HBeAg seroconversion
(No consensus for the non HBeAg seroconversion)

Monitoring
During treatment: Serial ALT, HBeAg and/or HBV DNA (non PCR) 1-3 monthly
After treatment: Serial ALT and HBeAg and/or HBV DNA (non PCR) 3-6 month
For non-responders: Further monitoring to recognise delayed response or to plan retreatment