Antiviral Therapy for Chronic Hepatitis B

Dr. Man-fung Yuen  MBBS (HKU), MD (HKU), PhD (HKU), MRCP (UK), FHKCP, FHKAM (Medicine)
Senior Lecturer
Division of Gastroenterology and Hepatology, Department of Medicine,
The University of Hong Kong, Queen Mary Hospital

Introduction

Total eradication of hepatitis B virus (HBV) in patients with chronic hepatitis B (CHB) infection is seldom achieved with the available agents to date. The present goal of treatment is to reduce the risk of development of cirrhosis-related complications and hepatocellular carcinoma (HCC) through continued suppression of HBV replication. For the purpose of clinical trials, relatively short-term endpoints are adopted. These include loss of hepatitis B e antigen (HBeAg) with or without seroconversion to antibody to HBeAg (anti-HBe), normalisation of serum alanine aminotransferase (ALT) level and histologic improvement as evident in liver biopsy.

This article will focus on the four FDA-approved drugs, namely interferon-alpha, lamivudine, adefovir dipivoxil and entecavir.

Interferon-alpha

Interferon-alpha (IFN-α) is the first approved drug for the treatment of CHB. The antiviral activity is mediated through an immunomodulatory effect by upregulating the MHC class I antigen expression of the infected hepatocytes. Another involved mechanism is the direct antiviral effect through activation of oligoadenylate synthetase to cleavage viral RNA. Conventional IFN-α is given as either 5 MU daily or 10 MU thrice weekly for 16 weeks. A meta-analytic study shows that IFN-α treatment results in higher chance of loss of HBeAg, undetectable HBV DNA and loss of HBeAg when compared with controls (33% vs. 12%, p<0.001; 37% vs. 17% p<0.0001; 8% vs. 2%, p<0.001, respectively).2 Because of prolonged CHB infection in Asians who acquire the disease in early life, the ALT levels are usually normal or only mildly elevated. Therefore, the response to IFN-α is generally poorer when compared to Caucasians. The long-term beneficial effects of IFN-α are still controversial. According to a meta-analysis, there is no preventive effect of HCC in patients with CHB receiving IFN-α.3 However, one study on Caucasian population shows that IFN-α reduces the chance of HCC.4 Another study from Taiwan with patients having high ALT levels (> 200 U/L) shows IFN-α though does not reduce the chance of cirrhosis-related complications, it reduces the risk of HCC.5 This finding is not confirmed by a larger study with longer follow-up in Hong Kong with patients with lower ALT levels (the usual ALT levels in Asian patients).6

With the new preparation of pegylated interferons, Pegintron® and Pegasys®, newer trials have been performed. In general, combination therapy with pegylated interferon and lamivudine has similar efficacy when compared to pegylated interferon monotherapy.7, 8 However, when compared to lamivudine monotherapy, pegylated interferon plus lamivudine or pegylated interferon alone has better efficacy. The results should be interpreted with caution because these studies limited the duration of lamivudine treatment to 48 weeks only. The standard duration of lamivudine therapy is not based on a fixed period of time but on the achievement of HBeAg seroconversion. Furthermore, the final efficacy results were determined 6 months after the lamivudine either as monotherapy or in combination with pegylated interferon, was stopped. This makes the comparison with pegylated interferon monotherapy difficult to interpret.

Lamivudine

Lamivudine is the prototype drug of nucleotide/nucleoside analogues. Its main action is mediated through suppression of HBV replication by inhibition of reverse transcriptase activity and DNA chain termination. One-year lamivudine treatment results in 16% of patients achieving HBeAg seroconversion, 72% of patients with normalisation of ALT, 98% reduction of HBV DNA levels, and 56% of patients with histological improvement.9 According to the follow-up study in the same Asian cohort, the cumulative HBeAg seroconversion rates are 22%, 29%, 43%, 45% and 50% for the first to fifth year, respectively.

According to two 3-year histologic studies,10, 11 lamivudine treatment is associated with reduced necroinflammatory activity, reversal of fibrosis and even reversal of cirrhosis in some patients. These beneficial effects are more pronounced in patients without lamivudine-resistant HBV.

Along the serologic, virologic and histologic improvement by lamivudine treatment, it has been confirmed that 3-year lamivudine treatment is associated with a significantly lower rate of disease progression compared to placebo (9% vs. 21% respectively, p=0.001). More importantly, lamivudine is able to reduce the rate of development of HCC after 3
years of treatment (5% for lamivudine group and 10% for placebo group, p=0.047).12

The outstanding advantage of lamivudine is the absolute safety profile in terms of clinical adverse event and of the use for patients with hepatic decompensation in which IFN-α treatment is contraindicated. However, the major drawback of lamivudine is the emergence of lamivudine-resistant HBV at the C domain of the HBV polymerase gene (YMDD to YIDD or YVDD). In spite of the fact that the YMDD mutants have less replication competency than the wild-type HBV, hepatitis flares resulting in hepatic decompensation may occur. The incidence is however less than 1% of patients.

**Adefovir dipivoxil**

According to the two large scale phase III multicentre, double-blind, randomised, placebo-controlled trials of 48-week treatment of adefovir dipivoxil in 515 HBeAg-positive and 185 HBeAg-negative CHB patients,13, 14 patients receiving adefovir dipivoxil had significant improvement of histology (53% and 64% of patients respectively), reduction of HBV DNA (3.5 and 3.9 logs reduction), higher chance of HBeAg seroconversion (12% for HBeAg-positive patients) and higher proportion of patients with normalisation of ALT (48% and 72% of patients respectively) when compared with placebo. At the dose of adefovir dipivoxil 10 mg daily, there is no renal toxic event observed after 48 weeks of treatment.

Continuation of adefovir dipivoxil treatment beyond 48 weeks is associated with increasing rate of HBeAg seroconversion and increasing chance of ALT normalisation. However, elevation of serum creatinine of ≥ 0.5 mg/dl is observed in approximately 4.5% of patients receiving adefovir dipivoxil at 10 mg by 144 weeks of treatment.

Adefovir dipivoxil is effective for both wild-type HBV and lamivudine-resistant HBV. It is also effective in pre- and post-liver transplant patients with lamivudine-resistant HBV with 90% of patients having improvement of Child-Pugh score.

Adefovir dipivoxil though has a lower chance of emergence of drug-resistant HBV compared to lamivudine, the rate increases with prolonged treatment (0%, 3%, 11% and 18% from first to fourth years) The mutations occur in B and D domains of the polymerase gene with rtA181V (alanine substituted by valine) and rtN236T (asparagine substituted by threonine) respectively. However, these mutants are susceptible to lamivudine treatment.

**Entecavir**

Entecavir is the newest nucleoside/nucleotide analogue approved by FDA. A phase II trial with 6 months duration of treatment demonstrates that entecavir (either at 0.5 mg or 1 mg daily) is superior to lamivudine in term of magnitude of viral suppression. In addition, entecavir at the dosage of 1 mg is effective against YMDD mutants. Two multicentre phase III trials recruiting HBeAg-positive and anti-HBe-positive patients are going to be published. For the trial of HBeAg-positive patients, 48-week entecavir treatment results in mean HBV DNA reduction of approximately 7 logs (69% of patient with HBV DNA levels below 400 copies/mL), 72% of patients having histologic improvement and 78% of patients having normalisation of ALT levels.15 For the trial of anti-HBe-positive patients, 48-week entecavir treatment results in a mean HBV DNA reduction of 5.2 logs (89% of patients with HBV DNA levels below 200 copies/mL), 70% of patients having histologic improvement and 86% of patients having normalisation of ALT levels.16 Although infrequent genotypic resistant viruses to entecavir has been identified, they are not associated with virologic breakthrough with no rebound of HBV DNA levels if they do not have pre-existing YMDD mutations.

**Conclusions**

Prolonged viral suppression is the goal for treatment of CHB disease. Several agents with different anti-viral potency, chances of emergence of drug-resistant virus and adverse events are available for CHB patients. Clinicians should consider these three properties of individual agent for individual patient in order to select appropriate agent for treatment which will be of long-term basis.

**References:**