Arch Clin Infect Dis. 2012 October; 7(4): 107-8. DOI: 10.5812/archcid.15385

Published online 2012 October 5. **Editorial**

New Advances in Treatment of Chronic Hepatitis B Infection

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Received: July 29, 2012; **Revised:** August 3, 2012; **Accepted:** August 16, 2012

Keywords: Hepatitis B; Tenofovir; Therapeutics

Hepatitis B virus (HBV) is a small non-enveloped DNA virus which is a member of the Hepadnaviridae family. Chronic HBV infection is estimated to affect more than 350 million people worldwide with over two billion people being exposed to the virus. Risk factors for the chronic infection include age of exposure to the virus, concurrent immunosuppression and HIV infection. Individuals chronically infected are 200 times more likely to develop hepatocellular carcinoma (HCC) than uninfected individuals who are at the risk of developing cirrhosis and decompensated liver disease (1). The consequence of exposure to hepatitis B virus (HBV) is either clearance or persistence of HBV surface antigen. The latter is referred to as chronic infection and is clinically defined as the presence of HBV surface antigen in the serum 6 months from the time of exposure. Acute exposure may be asymptomatic (at up to 70%), but may also be presented as either an acute hepatitis or rarely as fulminant hepatic failure. The subsequent risk of chronic infection is determined by a number of factors, of which the most important is the age of acquisition. Neonates born to mothers are in danger of developing chronic infection themselves of between 20% and 90% depending on the mother's hepatitis B, secreted e antigen (HBeAg) status and her level of HBV DNA viremia (2). Adult exposure usually leads to chronic infection in less than 5% of the exposed individuals. It is ultimately the strength and breadth of both the innate and the subsequent adaptive immune response which determine the host's outcome. This in turn may be ultimately determined by host and viral genetic determinants (3).

The goal of treatment of CHB is to prevent cirrhosis, hepatic decompensation and HCC leading to an improved quality of life and survival. The ideal endpoint of therapy is HBsAg loss. However, this is an infrequent occurrence with current therapies. Other clinically important end points are biochemical remission, HBeAg seroconversion and induction of sustained virological remission (undetectable HBV viraemia). These secondary endpoints should lead to histological improvement and a reduction in risk of HCC. Drugs available for the treatment of CHB currently include *IFN*, pegylated IFN and six Nucleos (t) ide analogues (NAs). Either drug class can be used in different phases of infection (1). The reasons for pegylated IFN therapy are either HBeAg seroconversion or an HBV DNA, 12 months post treatment of < 2000 IU/mL (if treating HBeAg-negative patients). In a multicentre, randomized, partially double-blind study (67 sites, 16 countries), 814 patients with HBeAg-positive CHB were accidental to either pegylated IFN alpha 2a (PIFN) plus oral placebo, PIFN plus lamivudine, or lamivudine alone (4).

Therefore, the benefits of PIFN include a defined period of therapy, a lower rate of viral resistance and the theoretical potential for immune-mediated virological control. In addition, there is a higher loss of HBsAg at 3% - 7%. It is however contraindicated in decompensated liver disease, autoimmune disease, uncontrolled severe depression/psychosis and pregnancy (4). A fourty-eight-week course is mainly recommended for patients. Pretreatment factors for predicting HBeAg seroconversion include an HBV DNA < 2 × 108 copies/mL, high serum ALT (2 - 5 × upper limit of normal [ULN]), HBV genotype (A/B > C/D) and moderate inflammation on liver biopsy. On-treatment predictors of seroconversion have also been identified. These include a fall in HBV DNA to < 20,000 IU/mL at week 12, ALT flares with a fall in DNA, an HBsAg titre < 1500 IU/mL at week 12 and possibly interleukin (IL) - 28 B polymorphisms (4).

Prolonged oral therapy with Nucleostide Analogues has been proven to induce a reduction in HBV DNA, resulting in an improvement in histology and liver biochemistry. For some patients, this may lead to HBeAg seroconver-

sion and possibly even HBsAg loss, also these drugs target the HBV polymerase, their prolonged oral therapy may lead to viral resistance with a resultant rise in HBV DNA titres (1). Lamivudine monotherapy has a high percentage of genotype resistance over time and is therefore not recommended as first-line monotherapy. Telbivudine also has a low barrier to resistance, and despite the table results, high incidences of resistance have been seen in patients with a high baseline HBV DNA. In a study, virologic breakthrough and incidence of resistance in HBeAg positive patient can be used as a single therapy on a long-term basis (5, 6). Entecavir has a high barrier to resistance. There have been several trials assessing the efficacy of entecavir. In another study, 474 CHB Nucleos (t) ide-naïve patients were given Entecavir with a follow-up period of four years.

The trial highlighted 96% undetectable HBV DNA, 42% HBeAg loss, 38% seroconversion and 93% ALT normalization by the fourth year. There was only a 0.4% resistance rate. No histological data were, however, available in this trial. Entecavir is therefore recommended as monotherapy. Resistance is rare, but is more likely to occur if there is preceding lamivudine resistance. In addition, a higher dose of drug is needed if there is preceding lamivudine resistance (7). Adefovir is less efficacious than Tenofovir, with well-described resistance patterns, hence Tenofovir is approved for single usage. Indeed, in a large phase III study of nucleoside-naïve patients (both HBeAg positive and negative) randomly assigned to receive either Tenofovir or Adefovir on a 2:1 basis, 76% of the patients on Tenofovir achieved undetectable HBV DNA, 68% had ALT normalization, 3% had HBsAg loss, 74% reduction > 2 in their necroinflammatory score without worsening of their fibrosis and a 21% HBeAg seroconversion. It also highlighted a 3% virologic breakthrough at 144 weeks (associated with poor compliance), but not viral resistance (8). It seems that Tenofovir with less described resistance pattern, easy use and high availability is an optimal option for treating of chronic hepatitis B infection in Iran.

Financial Disclosure

There is no conflict of interest.

Funding/Support

There was no financial support.

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