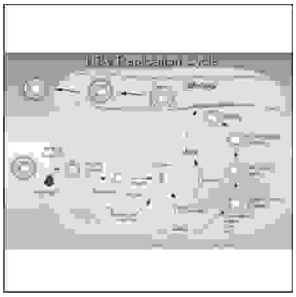
REVIEW PROF-1187

CHRONIC HEPATITIS B VIRUS INFECTION;
CURRENT TREATMENT AND FUTURE PROSPECTS



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ABSTRACT ... Hepatitis B virus is a major health dilemma causing an enormous burden on the health care system and a major source of patient's suffering. Over the last decade, far-reaching research has not only led to the enhancement of present management of chronic hepatitis B, but has also revealed new options for the treatment of this appalling disease. Presently interferon alpha- 2b, lamivudine, adenofovir dipivoxil and tenofovir are being employed for the management of chronic hepatitis B infection. However, extensive research is being carried out to assess the efficacy of peg- interferon, emtricitabine, entecavir and telbivudine in treating chronic hepatitis B infection.

Key words: Chronic hepatitis B infection. Current treatment. Future prospects.

INTRODUCTION

Treatment of chronic Hepatitis B virus infection has been a challenge for medical science since its discovery. Patients who are chronically infected with hepatitis B virus are at increased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma.Therapeutic intervention offers the only means of interrupting this progression. Each treatment modality has its own specific problems. Presently four drugs are being used for treatment of chronic HBV infection namely interferon alpha, lamivudine, adefovir and entecavir[1]. The dual action of tenofovir and emtricitabine against HBV and HIV provide a good choice of treatment in patients co-infected with both these viruses. Nucleotide analogue e.g, adefovir and tenofovir have much less chances of developing of resistance as compared to nucleoside analogue e.g. lamivudine and emtricitabine[1]. Although response to interferon alpha is not good in HBV/HIV co-infected patients, especially in hepatitis B antigen negative HBV infection, the under trial more potent pegylated interferon has brought in new hope[1]. Treatment options for chronic hepatitis B virus (HBV) infection have desparate risks and benefits. Interferon has clinically significant side effects, and lamivudine is associated with viral resistance. In contrast, adefovir is safe and has lower viral resistance but is more expensive. The most cost-effective approach is uncertain[2].

GENOTYPES

Currently eight genotypes of hepatitis B virus have been identified (A-H)[3]. Sub genotypes have been described in four of these genotypes (A,B,Cand F). These genotypes show a distinct geographical distribution between and within the regions[3].

TREATING CHRONIC HEPATITIS B VIRUS INFECTION

Only those patients who have chronic hepatitis B qualify for the treatment. Patients with chronic hepatitis B virus infection (HBsAg positive for >6 months), raised alanine transaminae level i.e more than 1.5 fold high than normal, hepatitis B virus DNA >10^5 copies/ml, and high histological activity index>4 are the most suitable candidates for treatment[4].

INACTIVE HBsAg CARRIERS

Inactive carriers usually do not need treatment. However Alanine transaminase level should be checked every 6-12 months. Screening for hepatocellular carcinoma should also be performed at regular intervals[4].

CIRRHOSIS

Patients with compensated cirrhosis need treatment as for those patients with chronic hepatitis B virus infection. However, the response to the treatment is poor as compared to the patients with chronic hepatitis B infection.In cases of decompensated cirrhosis treatment with lamivudine is indicated, with liver transplantation being the only other option[4].

GENERAL ADVICE

The patients suffering from chronic hepatitis B infection should be advised to avoid alcohol and to practice safe sex.Patients should be encouraged to reduce weight. People who might spread hepatitis at work should either undergo treatment or change their profession. Immunosuppressive drugs should be used with caution in order to avoid activating hepatitis B virus infection[4].

The drugs currently being used in the treatment of hepatitis B virus infection and that understudy are being described briefly as under:

INTERFERON ALPHA-2b

Interferon alpha-2b is still considered to be the drug of choice in treating chronic hepatitis B infection. It is administered to patients showing evidence of active viral replication including HBsAg, HBV DNA (more than 10 million copies / ml) and raised level of aminotransferases in the serum. The recommended dose of interferon alpha-2b is 5 million units daily or 10 million units three times a week intramuscularly for a period of four months. Interferon has been used in both types of chronic hepatitis B. In HBsAg positive patients, about a third show virological and histological response. Interferon induced responses are less durable in HBsAg negative chronic hepatitis B. Though prolonging treatment for one to two years may improve the sustained response rates, the benefit in these patients remains less than that in HBsAg positive chronic hepatitis B.

Interferon can have several adverse effects. An influenza-like illness (fever, chills, headache, malaise, myalgias) occurs in 25-30% of patients but rarely needs discontinuation of treatment. More serious adverse events (myelosuppression (leucocytes < 1000/µl and platelets < 60 000/µl), emotional liability and depression, development of autoantibodies, and thyroid dysfunction) may lead to discontinuation of interferon; thus, pretreatment screening for psychiatric illness, low leucocyte and platelets counts, autoantibodies, and thyroid function is mandatory[4].

LAMIVUDINE

The nucleoside analog lamivudine, may be used instead of interferon for treatment of chronic hepatitis B and is much better tolerated. This agent reliably suppresses HBV DNA in serum, improves liver histology. the response rate depends on duration of treatment: prolonged treatment is associated with higher seroconversion rates (21% at one year, 29% at two years, 40% at three years). However, with increasing duration of treatment, an increasing proportion of patients develop a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) motif in the catalytic domain of viral DNA polymerase, which confers lamivudine resistance (14% at one year to 69% at five years), which affects the

disease course adversely[4].

ADENOFOVIR DIPIVOXIL

Adenofovir Dipivoxil is a prodrug of adefovir , with potent antiviral activity against hepatitis B virus. It is given 10 mg daily for 48 weeks. Adenofovir shows activity against both hepatitis B e antigen positive and negative chronic hepatitis B infection[5,6]. It has been found to maintain its efficacy even after three years of therapy in chronic hepatitis B antigen negative infection[5,6]. Adenofovir dipivoxil can be used in compensated and decompensated chronic hepatitis B liver disease as well as in both pre and post transplant patients without significant side effects. The drug is associated with nephrotoxicity but the risk is low at the recommended dose[7]. Adenofovir dipivoxil results in delay of hepatic decompensation[8]. In patients with pre- existing cirrhosis and early switch to Adenofovir dipivoxil appears to be indicated after emergence of lamivudine resistance[8,9,10].

CO-INFECTION WITH HIV

Adenofovir dipivoxil is active against both HIV and HBV. Results indicate that 48 weeks of 10mg daily of Adenofovir dipivoxil is welltolerated and active against lamivudine-resistant HBV in HIV/HBV co-infected patients[11].

TENOFOVIR

Tenofovir disoproxil fumurate, a congender of adenofovir dipivoxil that is used in the treatment of HIV infected patients, has recently been shown to also be effective in patients with lamivudine–resistant HBV infection. Individually, all tenofovir- treated patients showed a strong and early suppression of HBV DNA within few weeks whether they are co-infected with HIV or without co morbidity. In conclusion, tenofovir may become an effective alternative for the treatment of patients with lamivudine – resistant HBV infection[12,13].

FUTURE PROSPECTS OF CHRONIC HBV INFECTION

Although medical science is still trying its best to find a satisfactory treatment for chronic HBV infection but results of drugs under use are far from satisfactory. Following drugs are being tested for their efficacy against chronic HCV infection and have shown good results and hope for better treatment results for chronic HBV infected patients.

PEG INTERFERON

To significantly improve the pharmacological properties of the drug, a pegylated form of IFNalpha(2a) was developed (PEGASYS). This 40 kDa PEG-conjugated IFNalpha(2a) ((40)PEG-IFNalpha(2a)) is obtained by the covalent binding of one 40 kDa branched PEG-polymer to a lysine side-chain of IFNalpha(2a)[14].Peg interferon has recently been introduced as potential treatment of chronic hepatitis B and hepatitis C virus infection[15].Peg interferon has higher efficacy than standard interferon and its tolerance is similar[16]. In patients with HBsAg positive chronic hepatitis B, peginterferon alfa-2a offers superior efficacy over lamivudine, on the basis of HBsAg seroconversion, HBV DNA suppression, and HBsAg seroconversion[17]. The superiority of pegylated interferon over recombinant interferon is remarkable especially in "hard to treat" patients cirrhosis[18]. In patients with chronic hepatitis B and compensated liver disease prolonged pegylated interferon alpha-2b therapy is safe, and that pre-existing cirrhosis and neutropenia are the most important predictors of dose reduction or early treatment discontinuation[19]. Pegylated interferon alpha-2b is effective for HBsAg positive chronic hepatitis B. Combination with lamivudine in the regimen used is not superior to monotherapy. HBV genotype is an important predictor of response to treatment[20].

ENTECAVIR

Entecavir, a new deoxyguanine nucleoside analogue, is selective inhibitor of replication of HBV[21]. An impressive reduction serum viral DNA has been observed with covalently closed circular DNA and hepatitis B viral core antigen negativity in liver biopsy specimens. In clinical studies, entecavir revealed excellent suppression of hepatitis B virus replication without significant side effects or evidence of mitochondrial toxicity. Until now no entacavir-resistant viral mutants have been described. Prolonged therapy as well as prophylactic therapy, for example, in liver transplant recipients, is feasible and not

limited by break through infections[22]. Entecavir has potent antiviral activity against HBV at 0.1-mg/day and 0.5-mg/day doses, both of which are superior to lamivudine in chronically infected HBV patients[23].

TELBIVUDINE

Telbivudine, beta-L-2'-deoxythymidine (LdT), is a new beta-L-nucleoside analogue with potent inhibitory activity against the hepatitis B virus. In vitro studies and animal models, telbivudine has demonstrated potent and specific antiviral activity against hepatitis B Additionally, in preclinical animal toxicology studies, telbivudine showed no adverse side effects or adverse effects on mitochondrial function[24]. Telbivudine was well tolerated with no identified safety issues. Virological breakthrough with telbivudine was significantly lower than with lamivudine[24].

EMTRICITABINE

Emtricitabine was well tolerated and demonstrated a potent antiviral response for up to 2 years in patients with chronic hepatitis B infection. Based on these data, 200mg emtricitabine once daily was chosen as the optimal dose for future hepatitis B studies[25]. Peak plasma emtricitabine concentrations occurred within 1.5 h following dosing. Plasma emtricitabine concentrations (maximum concentrations of drug in plasma and areas under the concentration-time curves) increased nearly dose proportionally over the 25- to 300-mg dose range, with relatively small intersubject variabilities. The plasma half-life of emtricitabine ranged from 6 to 9 h. HBV DNA levels were measured by the Digene HBV Hybrid Capture II assay. Viral suppression (reduction in log(10) serum HBV DNA levels) occurred in all dose cohorts. All doses demonstrated potent and rapid antiviral activities, with a trend toward a greater suppression with daily doses of 100 mg or greater. At 2 months, the median change in the serum HBV DNA level from the baseline level ranged from -1.7 log(10) for the 25-mg dose administered q.d. to -3.3 log(10) for the 300 mg dose administered q.d. Emtricitabine was well tolerated over the 2-month dosing period. These results support further clinical development of emtricitabine for the treatment of chronic hepatitis B infection[26].

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