THERAPY

Treatment of chronic hepatitis B in 2002

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Abstract

Viral hepatitis B is a serious health problem, above all in the world's developing countries. It is estimated that two billion people will be infected with the hepatitis B virus in the course of their lives and between 350 and 400 million people are chronically infected at present. The aims of the treatment of chronic hepatitis B are sustained suppression of viral replication and remission of liver disease. For the treatment of chronic hepatitis B two drugs have been licensed worldwide: alpha-interferon and lamivudine. In chronic hepatitis B therapy there are new developments in antiviral, such as nucleoside analogues – entecavir, emtricitabine, clevudine, beta-L-nucleosides. Studies comparing pegylated interferon with lamivudine and with the combination of lamivudine and pegylated interferon are in progress. Several innovative antiviral approaches have been evaluated *in vitro,* and in animal models of hepadnavirus infections. These approaches are including antisense oligonucleotides, ribozymes, inhibitors blocking virus entry into hepatocytes, and decoy virus or dominant negative mutants. *(Tab. 1, Ref. 25.)*

Key words: chronic hepatitis B, alpha-interferon, lamivudine, adefovir dipivoxil, nucleoside analogues, pegylated interferon.

Viral hepatitis B is now a serious health problem, above all in the world's developing countries. It is estimated that two billion people will be infected with the hepatitis B virus (HBV) in the course of their lives and that between 350 and 400 million people are chronically infected at present. Between one and two million people die annually as a direct result of HBV infection, suffering liver cirrhosis, hepatocellular carcinoma (HCC) or fulminant hepatitis. For these reasons, hepatitis B is the ninth leading cause of death in the world (Hoofnagle and Di Bisceglie, 1997; Lee, 1997; Lok et al, 2001; Lok and McMahon, 2001).

Clinical forms of HBV infection

Hepatitis B infection may be associated with a very large spectrum of clinical forms that may occur in subjects of any age and with different immunological status.

A. Acute hepatitis B

Acute hepatitis B is usually a benign disease showing spontaneous resolution and recovery in more than 90 % of cases. In 0.1–1 % of the patients the acute hepatitis may have a fulminant course with a high mortality.

B. Chronic hepatitis B

Chronic hepatitis B is defined as positivity of hepatitis B surface antigen (HBsAg) for more than 6 months. Chronic hepatitis B patients may show different patterns in terms of viral serum markers and virus activity (Raimondo et al, 2002).

1) HBsAg positive patients with persistently active viral replication.

These cases show levels of circulating viruses $>10^5$ copies/ml and can be easily recognized by searching for serum HBV nucleic acid (HBV DNA) by direct hybridization techniques. These patients can be hepatitis B "e" antigen (HBeAg) positive or negative. Both groups of patients have an indication for antiviral therapy.

2) HBsAg positive individuals with permanent or temporary suppression of viral replication.

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This group of chronic hepatitis is highly heterogeneous and comprises the following subjects:

a) Patients with hepatitis D virus (HDV) coinfection

HDV is one of the strongest inhibitors of HBV activity known so far. The treatment of these patients is highly problematic. Fortunately, hepatitis D is still very rare in Central and Western Europe.

b) Patients with hepatitis C virus (HCV) coinfection

HBV and HCV shares modes of transmission, and this combined infection occurs quite frequently, particularly among subjects with a high risk of parenteral infections (intravenous drug abusers, hemophiliacs). Dual infection by HBV and HCV may be associated with severe forms of chronic liver disease poorly sensitive to alpha-interferon (IFN) treatment and with a high risk of HCC development (Zarski et al, 1998).

c) Inactive HBsAg carriers

This represents a large number of HBV infected individuals worldwide, who normal liver biochemistry, and if a liver biopsy is performed, the histology is normal or reveals minimal changes. These carriers do not need antiviral therapy but they must be properly followed.

d) Patients with alternating active and non-active viral replication phases

The early identification of these patients among HBsAg carriers is of great clinical relevance since episodes of reactivation may have a fulminant course and patients are at a high risk of developing cirrhosis and HCC. Antiviral therapy starts in an active viral replication phase (Perrillo, 2001).

3) Occult HBV infection.

Many studies performed in the last two decades have clearly demonstrated that HBV infection may persist also in the absence of circulating HBsAg. This occult infection is mostly associated with individuals positive for antibodies to HBV antigens (anti-HBc and/or anti-HBs), but it also occurs in a considerable number of individuals negative for all markers of HBV infection. The essential question in occult HBV infection issue is whether or not it has any clinical impact. In this connection, its potential role in HBV transmission and as a risk factor for HCC development has been sufficiently documented, although many aspects in terms of the pathogenic mechanism and the frequency of occurrence still need to be clarified (Cacciola et al, 1999; Raimondo et al, 2000; Conjeevaram and Lok, 2001).

Tab. 1. Factors predictive of a sustained response to alpha-interferon in chronic hepatitis B patients.

Favorable factors	Unfavorable factors
Adult-acquired infection	Child-acquired infection
Absence of cirrhosis	Cirrhosis
HBeAg-positive	HbeAg-minus mutant
HDV antibody-negative	HDV antibody-positive
Low pretreatment serum HBV DNA	High pretreatment serum HBV DNA
High pretreatment serum ALT	Low pretreatment serum ALT
High histological activity	Low histological activity
Absence of immunosuppression	Immunosuppression
Female	Male

Legend: Explanation of all expressions in the text

Aims of treatment of chronic hepatitis B

The aims of treatment of chronic hepatitis B are to achieve a sustained suppression of HBV replication and remission of liver disease. The end points used to assess treatment response include normalization in serum alanine transaminase (ALT) level, undetectable serum HBV DNA by direct hybridization techniques, loss of HBeAg with or without detection of anti-HBe antibodies (in patients infected by HBeAg positive type of HBV), and improvement in liver histology (Lok and McMahon, 2001).

Standard treatment of chronic hepatitis B

For the treatment of chronic hepatitis B two drugs have been licensed worldwide: alpha-IFN and lamivudine. The third potent drug, adefovir dipivoxil, is currently approved only in the United States (since September 20, 2002).

Alpha-interferon

The concept of interferon is historically linked with viral interference – a phenomenon by which cells in culture or animals infected by certain virus are resistant to infection by another virus inoculated at the same time or immediately after the first. The possibility that the status of resistance might be mediated by a soluble factor released by infected cells was deduced from the experiments of Nagano and Kojima in 1950s. However, there is no doubt that IFN, as a soluble mediator of viral interference, was effectively discovered by Isaacs and Lindenmann in 1957 and those authors used the term "interferon" for the first time. Interferons (IFNs) have antiviral, antiproliferative and immunomodulatory effects. The recent classification of IFNs is based on the structure of their genes. There are four types of human IFNs – alpha, beta, gamma, and omega (Kontsek and Kontseková, 1998).

Therapy of chronic hepatitis B with alpha-interferon

Alpha-IFN has proved to be effective in suppressing HBV replication and in inducing remission of liver disease. Table 1 shows the factors influencing the results of treatment with alpha-IFN in patients with chronic hepatitis B. It is clear that the efficacy of alpha-IFN is limited to a relatively small percentage of highly selected patients. Alpha-IFN is administered by subcutaneous injections. The recommended dose in adults is 5 megaunits (MU) daily or 10 MU three times a week and in children 6 MU/m^2 three times a week with a maximum of 10 MU.

The recommended duration of the treatment in patients with HBeAg-positive chronic hepatitis B is 16 to 24 weeks. HBeAg seroconversion, either spontaneously or following alpha-IFN therapy, significantly reduces morbidity and mortality. Responders to alpha-IFN therapy have a significantly lower risk of developing cirrhosis and HCC (Lin et al, 1999). Alpha-IFN therapy is associated with a loss of HBeAg in 30–40 % patients. High

pretreatment ALT activity and low serum HBV DNA levels are the most important predictors of a response to alpha-IFN therapy. Virology response to the therapy is observed in less than 10 % of patients with normal ALT.

Current data suggest that patients with HBeAg-negative chronic hepatitis B should be treated for at least 12 months but it is not clear if longer duration of the treatment increases the rate of sustained response. HBeAg loss or seroconversion cannot be used as an end point to assess the response in these patients. Therefore, the response is usually defined as undetectable serum HBV DNA by direct hybridization techniques and normalization of the ALT level. The analyses of the results of trials on alpha-IFN in HBeAg-negative chronic hepatitis B are complicated by the heterogeneity not just of the disease, but also of the virus and study design. Results of four randomized trials involving 86 alpha-IFN treated patients and 84 controls showed that end-of-treatment response ranged from 38 % to 90 % in the treated patients compared to only 0 to 37 % in the controls. The 12-month sustained response varied from 10 % to 47 % (average 24 %) among treated patients and 0 % in controls (Lok and McMahon, 2001).

Lamivudine

Lamivudine, a pyrimidine nucleoside analogue, was developed as a reverse transcriptase inhibitor for use in human immunodeficiency virus (HIV) infection. It also has activity against HBV at lower concentrations. Lamivudine (2',3'-dideoxythiacytidine) is a minus enantiomer and this may explain the very low rates of side effects noted with this agent (Thomas et al, 2002).

Therapy of chronic hepatitis B with lamivudine

The recommended dose of lamivudine in adults with normal renal function (creatinine clearance >50 mL/min) and no HIV coinfection is 100 mg daily, orally. The dose in children is 3 mg/kg daily with a maximum dose of 100 mg daily. Dose reduction is necessary for patients with renal insufficiency. Patients with HIV coinfection should be treated with twice daily 150 mg in addition to the other anti-retroviral therapies.

The end point of the treatment for HBeAg-positive patients is HBeAg seroconversion. In general, lamivudine should be given for 1 year, as a shorter duration of the therapy is associated with a lower rate of HBeAg seroconversion. Treatment may be discontinued in patients who have completed one year of the treatment and have persistent HBeAg loss, anti-HBe detection, and serum HBV DNA undetectable by direct hybridization techniques on more than one occasion determined 2–3 months apart. The durability of response after cessation of the treatment is expected to be 70 % to 80 %.

Three clinical trials involving a total of 731 naive patients who received lamivudine for 1 year reported that HBeAg seroconversion occurred in 16 % to 18 % of patients compared with 4 % to 6 % of untreated controls (Lai et al, 1998; Dienstag et al, 1999; Schalm et al, 2000). Follow-up reports of the multicenter Asian study showed that HBeAg seroconversion rates increased with duration of treatment from 17 % at 1 year to 27 %, 33 %, and 47 % at 2, 3, and 4 years, respectively (Liaw et al, 2000; Leung et al, 2001). Pretreatment ALT activity has been found to be the most important predictor of the response. Pooled data from 406 patients, who had received lamivudine for 1 year, showed that HBeAg seroconversion occurred in 2 %, 9 %, 21 %, and 47 % of patients with pretreatment ALT within normal, 1–2 times normal, 2–5 times normal, and more than 5 times normal (Chien et al, 1999).

Lamivudine has been shown to benefit patients with HBeAg-negative chronic hepatitis B. Clinical trials have reported a 1-year response rate of 64 % to 70 %. However, the vast majority (about 90 %) of patients relapsed when the treatment was stopped. Therefore, the optimal end point of the treatment for HBeAg-negative chronic hepatitis B is unknown. Because of high rate of post-treatment relapse in patients who responded after 1 year of the treatment, a long duration of the treatment may be needed (Tassopoulos et al, 1999; Hadziyannis et al, 2000).

Selection of lamivudine-resistant mutants is the main concern with lamivudine treatment. The most common mutation affects the YMDD motif of the HBV DNA polymerase. Lamivudine resistance is usually manifested as breakthrough infection defined as a reappearance of HBV DNA in serum on two or more occasions after its initial disappearance. The clinical course of patients with lamivudine-resistant mutants is variable, and the long-term outcome remains to be determined. In some patients, emergence of these mutants may be accompanied by acute exacerbation of liver disease and rarely by hepatic decompensation. However, most patients who continue the treatment have lower serum HBV DNA and ALT levels compared with their pretreatment levels. The continued benefit may be related to the suppressive effect of lamivudine on the residual wild-type virus and the impaired replication capacity of the mutants. HBeAg seroconversion has still been reported in approximately 25 % of the patients who continued the treatment after the detection of lamivudine-resistant mutants (Lok and McMahon, 2001).

Adefovir dipivoxil

Adefovir dipivoxil is an oral prodrug of adefovir (formerly known as PMEA). Adefovir is a nucleotide analogue of acyclic purine nucleoside phosphonates, with broad-spectrum, potent activity against hepadnaviruses, retroviruses, and herpesviruses (Brosgart and Gibbs, 2000). The recommended 10 mg daily dose is safe and well tolerated. Clinical trials showed histologic improvement, inhibition of viral replication and biochemical remission in the majority of chronic hepatitis B patients, both HBeAg-positive, and HBeAg-negative. Adefovir is also effective against lamivudine-resistant HBV strains, while no evidence of resistance to adefovir has been detected to date (Hadziyannis and Papatheodoridis, 2002). Adefovir dipivoxil is now approved in the United States for the treatment of chronic hepatitis B in adults with evidence of active viral replication and persistent elevations in serum transaminases or histologically active disease.

Perspective treatments of chronic hepatitis B

Combination of alfa-IFN and lamivudin

This combination was evaluated in two clinical studies with different results (Schiff et al, 1998; Schalm et al, 2000). However, problems in the designs of these two studies prevent a definite conclusion concerning the efficacy of the combination therapy. Until further data are available, this combination is not recommended.

Pegylated interferon

Polyethylene glycol (PEG) is a water-soluble, nontoxic polymer that can be covalently linked to different proteins. Pegylation increases protein half-life by reducing renal clearance and proteolysis. Pegylation leads to the less antigenicity, increased solubility, and thermal as well as chemical stability of the base protein. Pegylated interferon (PEG-IFN) has a significantly increased plasma half-life and thus it can be administered only once a week. The preliminary results from a pilot clinical trial showed that more than twice as many patients receiving PEG-IFN alfa-2a responded compared with patients receiving standard alfa-IFN. Two further phase 3 trials are under way using PEG-IFN alfa-2a in HBeAg-positive and HBeAg-negative chronic hepatitis B patients. Both of these studies compare PEG-IFN with lamivudine and with combination of lamivudine and PEG-IFN (Cooksley, 2002).

New nucleoside analogues

In chronic hepatitis B therapy there are new and exciting developments in antivirals such as the nucleoside analogues. The following agents have shown to be promising in clinical trials:

Entecavir is a selective inhibitor of HBV DNA polymerase because it has little or no inhibitory effect on the replication of other DNA viruses such as herpes simplex and cytomegalovirus and RNA viruses such as HIV. Entecavir has been proven to be effective against lamivudine-resistant HBV mutants, although the activity is significantly lower with wild-type HBV.

Emtricitabine has antiviral activity against both HBV and HIV. Its role in the treatment of chronic hepatitis B may be limited by its structural similarity to lamivudine and hence the potential cross-resistance.

Clevudine has marked *in vitro* activity against HBV but not HIV. *In vitro* studies suggest that it may also be effective against lamivudine-resistant mutants.

Beta-L-Nucleosides represent a newly discovered class of compounds with potent, selective and specific activity against hepadnaviruses. They are not active against other viruses such as herpes viruses and HIV. It is not yet clear if these compounds are active against lamivudine-resistant HBV mutants.

Molecular approaches to the therapy of chronic hepatitis B

Several innovative antiviral approaches have been evaluated *in vitro* and in animal models of hepadnavirus infections. These approaches include antisense oligonucleotides, ribozymes, inhibitors that block virus entry into hepatocytes, and decoy virus or dominant negative mutants. Many of these agents are in the early stages of development, and their clinical utility is still uncertain (Lok, 2001).

Therapeutical vaccines for chronic hepatitis B

The correlation between strong, polyclonal T-cell responses to HBV antigens and recovery from the acute infection suggests that vaccines that stimulate T-cell responses may induce an improvement in the recovery from chronic hepatitis B. Approaches to improve therapeutic HBV vaccines include use of multiple HBV antigens, more immunogenic routes of delivery, or stronger adjuvants, use of T-cell rather than B-cell epitopes. Human studies have not yet shown evidence that vaccination promotes viral clearance or recovery from chronic hepatitis B (Lok et al, 2001).

Even at the turn of the millennium, the treatment of chronic hepatitis B represents a serious problem for modern medicine. A lot of goals have already been achieved to improve the prognosis for those suffering from this insidious and dangerous disease, but many more problems still await a solution. Until even more effective means to a cure or partial cure of this disease are found, there will always be large numbers of patients who will reach the terminal stages of the illness, where their only hope is a liver transplant. Huge sums of money have been and are being invested worldwide in the fight against HBV. Thus, some hope of a crucial turn in the success of our treatment efforts is justified.

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