Review

Treatment of hepatitis B

CHUN TAO WAI and ANNA S.F. LOK

Division of Gastroenterology, University of Michigan Medical Center, 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109-0362, USA

Chronic hepatitis B virus (HBV) infection affects approximately 350 million people worldwide. Treatment of chronic hepatitis B is aimed at sustained suppression of HBV replication and remission of liver disease. Currently, antiviral treatment is indicated for hepatitis B e antigen (HBeAg)-positive patients in the immune clearance phase, and for HBeAg-negative patients with evidence of active liver disease and continued high levels of HBV replication. Treatment is not recommended for patients in the immune tolerance phase or the inactive carrier state, due to lack of efficacy of current treatment. This review updates safety and efficacy data of interferon alpha and lamivudine in the treatment of chronic hepatitis B. Management strategies in different clinical scenarios and future treatments are also discussed.

Key words: chronic hepatitis B, treatment, interferon alpha, lamivudine

Introduction

Chronic hepatitis B (CHB) remains an important global health problem. There are approximately 350 million persons chronically infected with hepatitis B virus (HBV) worldwide.[1] During the course of chronic HBV infection, an estimated 15% to 40% of CHB patients would develop complications such as exacerbations of hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[2]

Ideally, the aims of treatment would be to eradicate the virus, to induce remission of liver disease, and to improve long-term outcome. However, virus eradication is unlikely to be an achievable goal. Even in patients who have recovered from HBV infection with hepatitis B surface antigen (HBsAg) seroconversion, low-level HBV DNA can be detected in the blood and liver using sensitive methods such as polymerase chain reaction (PCR).[3,4]

Thus, the therapeutic endpoints for hepatitis B treatment are: sustained suppression of HBV replication, as indicated by HBsAg and hepatitis B e antigen (HBeAg) loss, decrease of serum HBV DNA of an undetectable level by a non-PCR method, and remission of disease, as shown by normalization of alanine aminotransferases (ALT) and improvement in liver histology. It must be emphasized that HBsAg loss is seldom accomplished, and even when it occurs is frequently delayed. In addition, it is unclear what level HBV DNA should be suppressed to in order that durable response can be achieved and progression of liver disease can be halted if treatment is stopped. Improvement in liver histology, defined as a decrease in the histological activity index (HAI) by two or more points has been used as the primary endpoint in several major clinical trials of nucleoside/nucleotide analogs. However, interpretation of liver histology suffers from the possibility of sampling error, intra- and inter-observer variability, and the lack of linearity of grading and staging systems. Moreover, the clinical significance of a two-point decrease in HAI has not been validated, and its relevance may be dependent on the initial HAI.[5]

Phases of chronic hepatitis B

The course of CHB infection can be conceptualized as consisting of four phases (Table 1).[6] The first phase is the immune tolerance phase, characterized by lack of clinical symptoms, high levels of HBV DNA, normal

Table 1. Four phases of the course of chronic hepatitis B infection

Phase	ALT	Serum HBV DNA	HBeAg
Immune tolerance	Normal	High	Positive
Immune clearance	Elevated	High to low	Positive to negative
Inactive carrier	Normal	Low	Negative
Reactivation	Elevated	High	Negative

HBeAg, Hepatitis B e antigen

Table 2. General management of patients with chronic hepatitis B

1. Avoidance of:
- Heavy alcohol consumption
- Unprotected sexual intercourse with partners who are not vaccinated
- Sharing of needles or other items that potentially contain blood such as shavers or toothbrushes
- Donation of blood or organs

2. Screening of family members and sexual partners for HBV infection and vaccination of those who are seronegative

3. Patient education and long-term follow-up with regular testing of liver biochemistry and surveillance of hepatocellular carcinoma in high risk groups

ALT, and minimal histological activity. This phase is usually seen in children and young adults with perinatally acquired HBV infection. Treatment is not recommended, as response rates of current therapy are poor.[7]

The second phase is the immune clearance phase, characterized by HBeAg to anti-HBe seroconversion. During this phase, immune clearance of HBV occurs and the destruction of infected hepatocytes may be manifested as an increase in ALT level. Successful HBeAg seroconversion is usually accompanied by a decrease in HBV DNA to low or undetectable values, and the normalization of ALT levels. However, some patients fail to achieve spontaneous HBeAg seroconversion and continue to have prolonged episodes of elevated ALT levels and active disease in liver histology, with repeated hepatitis flares, leading to an increased risk of cirrhosis.[8,9] During this phase, patients should be monitored closely, and if spontaneous HBeAg seroconversion does not occur after 3 to 6 months of observation, treatment should be initiated.[10]

The third phase is the inactive carrier state, characterized by the presence of anti-HBe, normal ALT, and low HBV DNA levels that are only detectable by PCR assays. Treatment is not indicated, as viral replication is already suppressed by the host immune response.

Some patients go on to the fourth phase, during which there is reactivation of HBV replication, characterized by an increase in serum HBV DNA and ALT levels. HBeAg remains negative and, hence, this phase is also known as HBeAg-negative CHB.[11] Spontaneous remission is uncommon and, hence, treatment is generally indicated.

Management of patients with chronic hepatitis B

Patients with CHB should be counseled regarding lifestyle modifications and prevention of transmission (Table 2). Heavy use of alcohol (>40g/day) has been associated with elevation of aminotransferases and increased risks of developing cirrhosis and should be discouraged.[12,13] Potential spread of infection through unprotected sexual intercourse, childbirth, sharing of intravenous needles, and environmental contamination from a blood spill should be discussed. Household members, including spouses, offspring, siblings, and parents are at increased risk of HBV infection and should be screened. Vaccination is recommended if they are seronegative.[14]

Patients should also be educated on the natural history and potential long-term complications of chronic HBV infection. Life-long surveillance of HCC with both alpha-fetoprotein and ultrasonography should be considered in high-risk carriers, such as men above the age of 45 years, persons with cirrhosis, and individuals with a family history of HCC.

Drug treatment of chronic hepatitis B

Two therapeutic agents, interferon-alpha (IFNα) and lamivudine, are currently approved in many countries for the treatment of CHB.

Interferon-alpha

IFN-α, a potent cytokine with antiviral and immunomodulating actions, is produced in response to viral infection.[15,16]

Efficacy in HBeAg-positive chronic hepatitis B. Metaanalysis of randomized controlled trials involving patients with HBeAg-positive CHB showed a significantly higher response rate with IFN-α as compared with placebo. Losses of HBeAg and HBsAg were 21% and 6% more, respectively, in the IFN-α-treated patients.[17] Post-hoc analysis showed that the major pretreatment predictors of response were high ALT level, low HBV DNA levels, female sex, and greater degrees of activity on liver biopsy.[1] Long-term follow-up studies showed that response was durable in 76% to 94% of responders and was associated with more favorable clinical outcomes, in terms of liver-related complications and survival.[18–20]

Attempts to induce a high pretreatment ALT level with steroid priming prior to IFN-α failed to show any definite improvement in response.[21] Besides, steroid withdrawal in CHB patients may lead to acute exacerbation of hepatitis, which can be fatal in patients with marginal liver reserve. Hence, steroid priming is currently not recommended in clinical practice.

Extending the treatment duration of IFN-α from the standard 16-week duration has been attempted to improve the response rates of IFN-α. A European study comparing 16-week versus 32-week showed that longer duration of IFN-α improved response in some patients.[22]

Efforts have also been made to use a long-acting preparation of IFN-α (pegylated interferon) in the treatment of CHB. Attachment of a polyethylene glycol polymer to IFN-α decreases its clearance, prolongs serum therapeutic level, and can potentially enhance its efficacy. Clinical studies are currently underway and initial results are promising.[23]

Efficacy in HBeAg-negative chronic hepatitis B. Four randomized controlled trials involving 86 IFN-α-treated patients and 84 controls showed that the end-of-treatment response ranged from 38% to 90% in the treated patients compared with only 0% to 37% in controls.[24–27] However, the relapse rate was high. Long-term response was observed in only 20% to 25% of patients. These responders appear to have a 10% chance of subsequent HBsAg loss, as well as an improvement in survival.[28]

Adverse effects. Adverse effects of IFN-α include constitutional symptoms, such as myalgia, flu-like symptoms, and fever; neutropenia; thrombocytopenia; mood changes, such as irritability, anxiety, and depression; and exacerbation or unmasking of autoimmune diseases. In addition, flares occur frequently in patients treated with IFN-α, so it is contraindicated in patients with decompensated liver cirrhosis.[29]

Lamivudine

Lamivudine (3TC), a nucleoside analogue, is the $(-)$ enantiomer of $2',3'$-dideoxy $3'$-thiacytidine. It is phosphorylated to the triphosphate (3TC-TP) which competes with dCTP for incorporation into growing DNA chains, causing chain termination. This may occur during reverse transcription of the first strand of HBV DNA, and during synthesis of the second strand of HBV DNA. Lamivudine has also been shown to reverse the T-cell hyporesponsiveness to hepatitis B viral antigens observed in patients with CHB.[30]

Efficacy in HBeAg-positive chronic hepatitis B. Lamivudine is taken orally at a dose of 100 mg daily. A 12-month course of therapy resulted in HBeAg seroconversion in 16% to 18%, as compared with 4% to 6% in the placebo group.[31,32] The HBeAg seroconversion rate increased to 27% and 40% after 2 and 3 years of therapy, respectively.[33,34] Post-hoc analysis showed that pretreatment ALT was the strongest determinant for response. The rate of HBeAg seroconversion was 7% when pretreatment ALT was less than twice normal, 20% for ALT two to five times normal, and 42% for ALT more than five times normal.[35]

Preliminary reports suggest that 73% to 86% of patients remained HBeAg-negative after HBeAg seroconversion in clinical trials, but some responders who had early relapse were not included in these follow-up studies, so these results may be overly optimistic. A Korean group reported a relapse rate of 49% 2 years post-treatment.[36] A possible reason for this high relapse rate could be the short duration of lamivudine treatment (mean, 9.3 ± 2.9 months). The duration of lamivudine treatment after HBeAg seroconversion may be an important factor determining the durability of response.

Efficacy in HBeAg-negative chronic hepatitis B. Lamivudine has been shown to benefit patients with HBeAg-negative CHB, with virological response in 60%–70% after 12 months of treatment.[37–39] However, relapse was close to 90% upon discontinuation of a 12-month course of lamivudine. On the other hand, continuation of lamivudine was associated with the emergence of resistance with breakthrough infection.[40] The lack of sustained response after a finite course of treatment and the development of resistance with continuous treatment suggest that lamivudine monotherapy may not be the optimal treatment for HBeAg-negative CHB.

Adverse events. Unlike IFN-α, lamivudine is well tolerated, with no difference in adverse effects compared with placebo. However, there are problems associated with the use of lamivudine. Firstly, the durability of

response appears to be lower than that with IFN-α therapy, although definitive data are still lacking.

Secondly, prolonged use of lamivudine is associated with the selection of lamivudine-resistant mutants. Two principal mutations can confer such resistance: a methionine-to-valine or -isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase at position 204 and a leucine-to-methionine substitution at position 180 upstream of the YMDD motif.[41] The rate of development of such lamivudine-resistant mutants increases with the duration of lamivudine treatment. In a multi-center Asian trial, the cumulative rate of genotypic resistance to lamivudine increased from 17% at 1 year to 69% at 5 years.[42] High pretreatment HBV DNA and ALT levels were found to be predictive factors for the selection of lamivudine-resistant mutants.[43]

The emergence of YMDD mutants is associated with increases in HBV DNA and ALT levels. In general, the levels are lower than those pretreatment, which is likely due to suppression of the wild-type HBV by continuation of lamivudine.[44] Besides, histological improvement has been documented even in patients harboring YMDD mutants.[45] However, acute exacerbation occurs in about 40% of patients at a median period of 24 weeks. Although HBeAg seroconversion may occur after the development of lamivudine resistance, hepatic decompensation and, rarely, fatality have been reported in patients with lamivudine resistance.[46] Moreover, a recent report suggested that the initial histological improvement might be negated.[34]

Combination therapy

Combination therapy, i.e., concurrent or sequential treatment with more than one drug, offers many theoretical advantages over monotherapy with either IFN-α or lamivudine. In particular, using more than one drug that acts on different parts of the life cycle of the virus provides more effective inhibition of HBV replication and may diminish or delay the emergence of drug resistance.

Three multicenter trials using combination therapy of lamivudine and IFN-α have been reported.[47–49] In the first two trials, involving 226 and 238 subjects, patients were given 8 weeks of lamivudine 100 mg daily, followed by 16 weeks of lamivudine 100 mg daily and IFN-α 10 MU thrice weekly. The results of combination treatment were not significantly better than those with monotherapy with either agent alone. Criticisms of these trials include the timing of IFN-α administration 8 weeks after the commencement of lamivudine and the short duration of lamivudine (24 weeks), as well as the timing of repeat biopsy (during versus 28 weeks post-treatment). In the third trial, involving 151 subjects,

patients were given 24 weeks of IFN-α 9 MU thrice weekly, together with lamivudine 100 mg daily, or 52 weeks of lamivudine, 100 mg daily. The rate of sustained response was significantly better in the combination group than in the lamivudine monotherapy group (33% vs 15%; $P = 0.014$). Further studies are needed to resolve these discrepant results. These studies will determine the efficacy of combination therapy of lamivudine and IFN-α using an optimal regimen, including the use of pegylated IFN.

Other combination studies using two nucleoside analogues, lamivudine-famciclovir and lamivudine-adefovir dipivoxil, showed promising results in viral kinetic studies.[50,51]

Other immunomodulators

Patients with chronic HBV infection have weak and restricted T-cell response to HBV antigens. Hence, therapy that stimulates immune response alone or in combination with antiviral agents may be effective in the treatment of CHB.

Thymosin-α, a bovine thymus extract, has been shown to improve T-cell function in in-vitro studies.[52] A recent metaanalysis involving five clinical trials and 353 patients showed a statistically significant delayed benefit.[53] However, there was marked heterogeneity among the five trials, and two of the trials analyzed were published only in abstract forms. Thus, more studies are needed before thymosin-α can be recommended for the treatment of CHB.

Other potential immunotherapies include therapeutic vaccines and interleukin-12.[54,55]

Other nucleoside analogues

Success in lamivudine spurred the search for other nucleos(t)ide analogues.

Adefovir dipivoxil is the oral prodrug of an acyclic nucleotide monophosphate analogue, a selective inhibitor of viral polymerases and reverse transcriptases with broadspectrum antiviral activity against retroviruses, hepadnaviruses, and herpesviruses.[56,57] Importantly, in-vitro studies showed that adefovir dipivoxil was effective against both wide-type and lamivudine-resistant HBV.[58]

In clinical trials, 12 months of adefovir dipivoxil 10 mg daily was associated with significant response in patients with HBeAg-positive CHB (12% HBeAg seroconversion vs 6% in the placebo group), as well as in HBeAg-negative CHB (51% virological response vs 0% in the placebo group).[59] In another study, involving 265 patients with lamivudine-resistant HBV, adefovir dipivoxil 10 mg daily was associated with a median drop of HBV DNA by 3.5 log at week 24 and 4.0 log at week 48, as well as clinical improvement in terms of liver

function.[60] More importantly, unlike lamivudine, there has been no report of adefovir dipivoxil-resistant forms of HBV.[61] In trials of adefovir dipivoxil in HIV patients, at a daily dose of 120 mg, renal toxicity (defined as a rise of serum creatinine >0.5 mg/dl from baseline) started to appear after 24 weeks and approached 50% by week 80.[62] The 10-mg daily dose in trials of CHB has not been shown to cause any nephrotoxicity. However, it would be prudent to collect more safety data from long-term follow-up studies.

Although the response of adefovir dipivoxil was modest as monotherapy, its potential is great as combination therapy with lamivudine or IFN-α for treatment-naïve patients with CHB and as salvage therapy for patients with lamivudine-resistant HBV.

Many other oral nucleoside analogues are also currently in their phase II or phase III clinical trials for the treatment of CHB, e.g., emtricitabine, entecavir, β-L-2′-deoxythymidine, val-d-cytosine. Some of these have also shown antiviral activity against YMDD mutants in vitro.[63,64]

Use of antiviral agents according to clinical setting

As mentioned earlier, the current antiviral agents, IFN-α and lamivudine, are not indicated in the immune tolerant and the inactive carrier phase.

HBeAg-positive chronic hepatis B. Because clinical studies of both IFN-α and lamivudine have revealed that pretreatment ALT level is an important predictor of response, it would be logical to offer treatment to patients in the immune clearance phase who do not achieve spontaneous HBeAg seroconversion after they have been observed for 3–6 months. Currently, treatment is only recommended to patients with active liver disease (ALT > two times upper limit of normal). Attending physicians should individualize treatment, after detailed discussion of the pros and cons of both agents with the patient, before starting treatment.

IFN-α is usually given subcutaneously for 16 weeks, in doses of either 5 MU daily or 10 MU three times per week. As mentioned earlier, longer duration of treatment was associated with better response in some patients. Future studies should evaluate the efficacy of a longer course of pegylated interferon in the treatment of CHB.

Lamivudine is given orally at a dose of 100 mg daily. A higher dose, 150 mg twice a day, in association with other antiretroviral therapy, is needed for patients with HBV and HIV co-infection. Dose reduction is recommended for patients with impaired renal function. The optimal duration of lamivudine treatment has not been established. Cessation of lamivudine shortly after HBeAg seroconversion is associated with a high relapse rate. A recent retrospective analysis from Korea showed that HBV DNA levels of more than 4700 copies/ml at the time of HBeAg seroconversion were associated with a higher rate of relapse.[65] However, further studies are needed to confirm this observation. In patients who are still HBeAg-positive at month 12, continuation of lamivudine for another 12 months increased HBeAg seroconversion from 17% to 27%.[34] However, the additional 12 months of treatment also increased the rate of YMDD mutants, from 14% to 40%. Discontinuation of lamivudine before HBeAg seroconversion leads to the return of HBV DNA to pretreatment levels and has been reported to be associated with a flare of aminotransferases in about 17% of patients. Mortality from hepatic decompensation has been occasionally reported.[66] In deciding whether to continue lamivudine in patients who fail to develop HBeAg seroconversion after 1 year of treatment, attending physicians must balance the benefit of increased response with longer duration of treatment and the increased rate of emergence of YMDD mutants.

For patients who have developed YMDD mutants, discontinuation of lamivudine leads to the re-emergence of wide-type HBV and the return of HBV DNA and ALT to pretreatment levels. In a follow-up study from Taiwan, hepatitis flares occurred in 40% of patients with YMDD mutants at a median duration of 24 weeks after the emergence of YMDD mutants. Among patients with YMDD mutants, 8/12 patients with a flare, compared with 0/19 without a flare, developed HBeAg seroconversion.[67] Concerns about relapse after treatment withdrawal and reports of HBeAg seroconversion in patients maintained on lamivudine after the emergence of YMDD mutants, and in-vitro studies showing that the YMDD mutants have decreased replication fitness have prompted recommendations to continue lamivudine in patients who have developed resistance. However, recent reports showed no difference in hepatitis flares, decompensation, or HBeAg seroconversion between patients who continued or discontinued lamivudine after the emergence of YMDD mutants.[68] These data should prompt re-evaluation of the recommendation on the management of patients with lamivudine resistance. As new antiviral agents with efficacy against lamivudine-resistant HBV, such as adefovir dipivoxil, become available, it is envisioned that most patients with lamivudine resistance, in particular those with evidence of worsening liver disease, should be switched to these new therapies.[60]

Table 3 compares the pros and cons of IFN-α and lamivudine. However, it should be noted that most trials involving IFN-α defined "response" as HBeAg loss, whereas trials involving lamivudine usually defined "response" as HBeAg seroconversion, i.e., HBeAg loss with appearance of anti-HBe.

Table 3. Pros and cons of interferon-alpha and lamivudine

	Interferon-alpha	Lamivudine
Pros	Finite duration of treatment: 4 months	Less expensive (if given for 1 year only)
	Not associated with selection of resistant mutations	Minimum adverse effects
	More durable response	Oral therapy
Cons	Considerable side effects during therapy	Duration of treatment may be prolonged
	Expensive	Emergence of resistant HBV with unknown long-term clinical consequences
	Subcutaneous administration	Less durable response

Direct head-to-head comparison of these two agents in treatment-naïve patients came from a study comparing lamivudine monotherapy, IFN monotherapy, and lamivudine/IFN combination therapy.[47] In that study, a 16-week course of IFN-α and a 1-year course of lamivudine resulted in HBeAg seroconversion in 19% and 18%, respectively, indicating that both agents are equally effective in the treatment of HBeAg-positive CHB.

HBeAg-negative chronic hepatitis B. IFN-α and lamivudine have been evaluated in the treatment of patients with HBeAg-negative CHB. However, HBeAg loss or seroconversion cannot be used as a therapeutic endpoint. Sustained response is generally defined as loss of HBV DNA by unamplified assay, with normalization of ALT 12 months after cessation of therapy.

Both IFN-α and lamivudine appear to have similar rates of response—60% to 70%—at the end of 1 year of treatment. However, the durability of response after cessation of treatment was only about 20% with IFN-α and less than 10% with lamivudine. Hence, longer duration of treatment may be required. But IFN-α is associated with significant side effects, and the prolonged use of lamivudine is associated with an increasing rate of drug resistance, which may ultimately negate the initial benefits. Thus, better treatment is needed.

Treatment of patients with decompensated HBV cirrhosis

The only curative treatment in this situation would be liver transplantation.

IFN-α is contraindicated in patients with decompensated cirrhosis, as flares of ALT during the course of IFN-α therapy may precipitate acute worsening of liver functiion.[10] Lamivudine treatment does not cause the usual adverse effects of IFN-α, such as ALT flares, neutropenia, or thrombocytopenia. Lamivudine has

been studied in patients with decompensated cirrhosis in the hope that the suppression of HBV replication will result in decreased hepatic inflammation and improvement in liver function. In addition, decreasing viral load pretransplant may reduce the risk of recurrent hepatitis B post-liver transplant. A pilot, uncontrolled study in 35 patients showed that, in patients receiving more than 6 months of lamivudine, liver function, including serum albumin level and the Child-Pugh score, improved.[69] Another retrospective study, reviewing 309 patients awaiting liver transplantation, confirmed that lamivudine was beneficial in a subset of patients.[70] However, many issues, especially the timing of treatment, need to be resolved before recommending lamivudine for patients with decompensated HBV-related liver cirrhosis. Cessation of treatment may lead to hepatitis flares, while prolonged use of lamivudine may lead to the emergence of YMDD mutants and worsening of liver disease.[66,67] Whether adefovir would be a better first-line treatment in these patients depends on its long-term safety profile, especially its nephrotoxicity.

Summary

Significant advances have been made in the treatment of CHB, but long-term response is still limited. Future treatment of CHB is likely to require combination therapy. However, many issues, e.g., which agents to use and in what form of combination, remain to be determined. In addition, combination therapy must demonstrate increased efficacy with no added adverse effects and minimal additional cost.

In conclusion, physicians treating patients with CHB must understand the natural history of CHB and the treatment options. Currently, antiviral treatment is indicated for HBeAg-positive patients in the immune clearance phase, and for HBeAg-negative patients with evidence of active liver disease and continued high levels of HBV replication. Treatment is not recommended

for patients in the immune tolerance phase or the inactive carrier state, due to lack of efficacy of current treatment.

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