



The "return" of hepatitis B

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Abstract

There has been a significant advance in the treatment of chronic Hepatitis B virus (HBV) infection and the following drugs were approved for therapy: Conventional interferon (IFN), pegylated interferon alfa-2a (PEG IFN α 2a), lamivudine, adefovir and entecavir. Compared to nucleoside analogues IFN induces higher rates of sustained remission and HBsAg loss. Conventional IFN in lower doses (1, 5-3 MIU) tiw for 4-6 mo has similar efficacy in comparison to "standard IFN therapy". Longer IFN treatment is a significant factor for long-term remission in HBeAg-negative CHB, but the higher actual IFN dose is not such a factor. PEG IFN is superior to conventional IFN. There is no significant difference between PEG IFN α 2a at doses 90 mcg/wk and 180 mcg/wk in HBeAg-positive patients. These results provide a rationale for further clinical trials with lower doses PEG IFN α 2a given in prolonged course as maintenance or intermittent treatment. Serious new problems arose after the introduction of nucleoside/nucleotide analogues in clinical practice. The most important ones are drug-resistance and the high rates of relapse after treatment discontinuation. Therapy should only be recommended if the expected benefit exceeds significantly the abstain from treatment. The choice of therapy should take into account the patient's age, co-morbidity, severity of liver disease and the risk of drug-resistance. New antivirals significantly suppress HBV-replication, but have no effect on cccDNA in hepatocytes, and after the treatment discontinuation viral relapses occurs. At the present level of knowledge it is impossible "to eradicate the virus" The realistic treatment goal is to achieve durable response by clearance of HBeAg, sustained decrease of serum HBV DNA levels, normalization of ALT, improvement of liver histology and stopping of liver fibrogenesis. The competition between IFN based therapy and nucleoside or nucleotide analogues still remains. IFN can cure the liver disease while nucleotide analogues only suppress the viral replication during therapy and can reduce the liver fibrosis. Treatment should be prolonged for 24-mo or longer by using maintenance or intermittent treatment course with the lowest effective IFN and PEG IFN

doses. Nucleoside/nucleotide analogues are a promising treatment option, but additional data for treatment duration and long-term post-treatment outcome are necessary.

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Key words: Chronic Hepatitis B virus infection; Interferon; Pegylated interferon; Low-dose therapy; Cyclic treatment

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem. This infection is especially endemic in Asia, South Pacific Region, sub-Saharan Africa and South America^[1]. It is estimated that over 350 million people worldwide are chronically infected with HBV and up to one million die annually due to HBV-related complications, including hepatocellular carcinoma (HCC)^[2]. In China and sub-Saharan Africa HCC associated with HBV is one of the leading causes of cancer in men^[1].

In the mid-1980s, IFN became the first approved therapy for CHB. In addition effective vaccines against HBV became available and there was a flicker of hope that the problem can be solved. Over the years it became clear that the chronic HBV infection is much more severe and difficult to treat disease than previously supposed. The positive impact of routine infant HBV-immunization programs is beyond doubt, but chronic HBV-infection still remains an important public health issue.

During the last decade much was learned about the HBV genome organization, viral replication cycle, role of host immune response and natural course of chronic HBV infection^[3]. The emergence of human immunodeficiency virus (HIV) infection on the other hand facilitated the search for effective and safe antiviral agents. Several new drugs were found to be quite promising candidates for the treatment of CHB. All these findings led to the 'return' of research interest in the treatment of CHB. A large number of clinical trials with new long-acting pegylated interferons (PEG IFN) and antiviral agents were performed. As a result of this intensive clinical research now we have five approved drugs for the treatment of CHB: Conventional IFN, PEG IFN α 2a as well as three nucleoside or

Table 1 Treatment response at the end of 24-wk follow-up after 24-wk therapy with IFN α 2a 4.5 MIU tiw, 90 mcg/wk, 180 mcg/wk and 270 mcg/wk PEG IFN α 2a (Adapted from W Cooksley *et al*^[12])

Response at the end of the 24-wk follow-up	4.5 MU IFN (n = 51)	90 μ g PEG IFN α 2a (n = 49)	180 μ g PEG IFN α 2a (n = 46)	270 μ g PEG IFN α 2a (n = 48)
HBV DNA < 500 000 cp/mL	13 (25%)	21 (43%)	18 (39%)	13 (27%)
Loss of HBeAg	13 (25%)	18 (37%)	16 (35%)	14 (29%)
HBeAg seroconversion	13 (25%)	18 (37%)	15 (33%)	13 (27%)
Normal ALT	13 (25%)	21 (43%)	16 (35%)	15 (31%)
Combined response ¹	6 (12%)	13 (27%)	13 (28%)	9 (19%)

¹HBeAg-negative, HBV DNA < 500 000 cp/mL, Normal ALT.

nucleotide analogues (lamivudine, adefovir and entecavir). Furthermore, several new drugs are under investigation in phase II and III clinical trials: emtricitabine, tenofovir, clevudine and telbivudine. Nevertheless, the treatment of chronic HBV infection is still a challenge due to the low rates of durable response with currently available therapies, especially in HBeAg-negative patients. The main problems with current treatments now are associated with suboptimal efficacy, poor tolerability, and/or emergence of resistance.

There are no clinical trials comparing directly the efficacy of all discussed therapies. Furthermore, it is difficult to compare the results of clinical trials in CHB due to the different sensitivity of the assays used for detection of serum HBV DNA over the years. In the early 1980's the virological response was measured only by serological assays (HBeAg and anti-HBe Ab). Later it became clear that the presence and absence of HBeAg is not an accurate indicator of replicative and nonreplicative infection and low-sensitive hybridization assays (detection limit of approximately 10^6 copies/mL) were developed for the measurement of serum HBV DNA^[3]. In the last years the majority of laboratories moved from hybridization techniques, through bDNA, to high-sensitive PCR (Roche Amplicor monitor) and RT PCR assays with lower detection limits of 10^3 copies/mL and < 100 copies/mL, respectively.

CURRENTLY APPROVED THERAPIES FOR CHRONIC HEPATITIS B

In spite of the mentioned difficulties, the treatment results of the approved therapies for CHB have been summarized by M Osborn and A Lok^[4,5]. Available data suggest that higher rates of sustained remission and HBsAg loss can be achieved with interferon based treatment in comparison to nucleoside analogue therapy.

IFN and pegylated interferons in HBeAg-positive CHB: Standard and low-dose treatment schedules

Conventional IFN has been used in CHB patients for 20 years. IFN has both antiviral and immunomodulatory effects^[6], but only 1/3 of HBeAg-positive patients achieve HBV DNA and HBeAg loss after 4-6 mo course of IFN at a dose of 5 MIU daily or 9-10 MIU thrice weekly^[7]. Subsequently, 6 to 12 mo post therapy HBsAg loss was found only in 8% of HBeAg-positive patients^[7]. These

treatment doses and durations have been validated as a "standard IFN therapy" for HBeAg-positive CHB by both EASL and AASLD treatment guidelines^[8,9]. However, some studies in HBeAg-positive patients suggested that conventional IFN, given in lower doses (1, 5-3 MIU thrice weekly) for 4-6 mo, is with similar efficacy compared to "standard IFN therapy"^[10,11]. This low-dose therapy is much better tolerated than higher IFN doses. Although treatment with low-dose IFN has not been generally accepted, these results are quite interesting especially in the light of new-coming data for the efficacy of PEG IFNs. A phase II clinical trial showed that PEG IFN α 2a is superior to conventional IFN in HBeAg-positive CHB^[12]. In addition no significant difference was found in PEG IFN α 2a efficacy given in dose of 90 mcg/wk in comparison to dose of 180 mcg/wk (Table 1)^[12].

Having in mind that the majority of the side effects of PEG IFN α 2a are dose-related, these results provide a rationale for further clinical evaluation of lower dose of PEG IFN α 2a as well as for new clinical studies with individualization of treatment schedule by PEG IFN tapering therapy. This might be a possibility to achieve better tolerability and lower treatment costs without losing the treatment efficacy. Further investigations are needed to confirm or reject this hypothesis.

IFN and pegylated interferons in HBeAg-negative CHB: standard and low-dose treatment schedules

Early clinical trials in HBeAg-negative CHB, with 5-10 MIU of conventional IFN for 4-6 mo reported high (60%-90%) end-of-therapy response (ETR), but only 10% sustained response (SR) due to frequent relapses after the therapy^[13]. Similarly to HBeAg-positive patients, HBeAg-negative subjects are sensitive to lower doses (1,5-3 MIU) of conventional IFN, but the relapse rate after 6-mo treatment course with low dose was also high^[14,15].

Mathematical models of chronic HBV infection indicate that, although the half-life of HBV is short (< 1 d), the half-life of hepatocytes is relatively long (10-100 d) or even higher for the infected hepatocytes^[16]. Therefore viral suppressive therapy might be continued for 1-10 years for viral elimination^[16]. Subsequently, a longer course with conventional IFN was reported to improve the SR, which was found to be 11% and 22% after 6 and 12 mo of conventional IFN therapy, respectively^[17]. Only the longer IFN course was identified as a significant factor of long-term remission, while the higher actual IFN dose was

not^[17]. An Italian study showed a 30% SR after a 24-mo maintenance course with 6 MIU IFN α 2a^[18]. However, this prolonged treatment was associated with poor tolerability of IFN and high incidence of dose-related adverse events. In a recent pilot study we found similar SR by using approximately 2-year cyclic therapy with low-dose (1.5 MIU) conventional IFN therapy^[19]. Taken together, this findings suggest that prolonged treatment (24-mo or longer) with conventional IFN in low-dose (1, 5-3 MIU) given as a maintenance or intermittent treatment course is appropriate therapeutic approach for HBeAg-negative CHB.

Recently, the efficacy of IFN-based therapy in CHB was improved by the introduction of PEG IFNs. In HBeAg-negative patients a 36% SR (combined biochemical and virological) was found at 6 mo after the 12-mo therapy with PEG IFN α 2a^[20]. However, 24-mo after the end of the treatment only 41% of patients with normal ALT levels 6-mo post therapy remained with combined biochemical and virological response^[21]. Our results with cyclic (re-induction) treatment^[19] provide a rational for further clinical trials with low-dose intermittent PEG IFN therapy in responders of 12-mo PEG IFN α 2a treatment. We have just initiated such a study aiming to test the potential of this treatment approach for reducing the relapse rate in end-of-treatment PEG IFN responders.

Lamivudine

Lamivudine was the first introduced nucleoside analogue in clinical practice. Twelve-month course with lamivudine induces HBeAg-seroconversion in 17% to 22% of the patients^[22-24]. HBeAg-seroconversion rates increased to 50% after continuous treatment for 5 years, but this was associated with increasing rates of drug-resistant mutations (up to 70%) after 5-year therapy^[25]. One-year lamivudine therapy suppressed viral replication in 65% to 90% of HBeAg-negative patients^[26,27]. However more than 90% of HBeAg-negative responders at the end of 12-mo course relapsed after treatment discontinuation^[27]. Extended treatment duration was associated with decreased response rate due to drug-resistance^[28]. The main concerns with lamivudine treatment are the selection of drug-resistant mutations and the very high relapse rate after treatment discontinuation. Both drug-resistance and relapse are associated with risk of hepatic flare and liver failure. Due to these reasons it is not recommended to use lamivudine as a first line therapy, especially in young patients. It should be also stressed that recent studies show PEG IFN α 2a monotherapy to induce higher SR rate in both HBeAg-negative and HBeAg-positive subjects in comparison to 1-year course with lamivudine^[20,29]. Combined therapy with lamivudine plus PEG IFN α 2a is with efficacy, similar to that of PEG IFN α 2a monotherapy^[20,29]. According to the current knowledge there is no biological rational for further use of this combination, but the consequent treatment with antivirals and IFN-based treatment is a possible treatment approach.

Adefovir

Recently, adefovir and entecavir were approved in the United States. Adefovir is effective in both HBeAg-

positive and HBeAg-negative patients^[30,31]. However, only 8% of the patients had a SR one year after treatment discontinuation^[32]. Adefovir effectively suppress lamivudine resistant mutants which is a significant advantage of this drug. Because of the high rates of drug-resistance, patients on prolonged lamivudine therapy need to be closely monitored. If virological breakthrough occurs due to drug-resistance, adefovir can be administrated in addition to lamivudine. Resistance to adefovir is uncommon during 2-year therapy, but emerge later in the course of treatment to 30% after 5-year therapy. Thus drug-resistance will be an increasing concern with longer adefovir treatment duration. Nephrotoxicity is another disadvantage of this drug.

Entecavir

Entecavir is more potent than lamivudine in suppressing HBV replication with significantly higher rates of biochemical and histological responses both in HBeAg-negative and HBeAg-positive patients^[33,34]. No entecavir-resistance was observed after 2 year therapy among nucleoside analogue naïve patients^[35]. However, the presence of lamivudine resistance increases the likelihood of entecavir resistance^[35,36]. Long-term data with entecavir still are not available.

NEW PROMISING ANTI-VIRAL AGENTS

Many new antivirals are under evaluation for the treatment of CHB. Emtricitabine (FTC) and tenofovir are licensed for use in HIV infection.

Emtricitabine

FTC is closely related structurally to lamivudine and therefore they share similar mutational sites^[37]. A recent study in HBeAg-positive and HBeAg-negative patients found that 48 wk of treatment with emtricitabine 200 mg daily resulted in significant histological, virological, and biochemical improvement^[38]. The results of emtricitabine treatment were quite similar to published data for lamivudine. The incidence of YMDD mutations in patients, receiving emtricitabine 200 mg daily, is 12% and 19% at treatment wk 48 and 96, respectively^[37,38]. The role of emtricitabine as a monotherapy may be limited due to its structural similarity to lamivudine and the risk of development of drug resistance.

Tenofovir

Tenofovir is an acyclic nucleotide inhibitor of HBV polymerase and HIV reverse transcriptase with close chemical similarity to adefovir^[37]. Antiviral activity of tenofovir against HBV is found to be greater than the one of adefovir 10 mg in lamivudine resistant patients^[37,39]. Furthermore, the N236T mutation that confers resistance to adefovir is sensitive to tenofovir^[37]. Phase III clinical trials are under way to determinate the long-term safety and efficacy of tenofovir.

Clevudine

Clevudine is a nucleoside analog of the unnatural β -L configuration. A recent randomized, double-blind study

found no significant difference between 24-wk therapy with emtricitabine plus clevudine and emtricitabine alone^[40]. However, there was a significantly greater virologic and biochemical response at wk 24 after the end of treatment in the emtricitabine plus clevudine arm^[40]. Further studies are needed to assess the long-term efficacy and safety of this drug.

Telbivudine

Telbivudine (LdT) is another antiviral agent, which is under clinical investigation in CHB. A phase II study in 104 HBeAg-positive patients compared different therapeutic schedules for 52 wk^[41]. The telbivudine-treated patients exhibited significantly greater virological and biochemical response in comparison to lamivudine^[41]. Results from the combined regimens (LdT plus lamivudine) were similar to those obtained with LdT alone^[41]. These data support the ongoing phase III evaluation of telbivudine for the treatment of CHB.

ADVANTAGES, DISADVANTAGES AND TREATMENT LIMITATIONS OF CURRENT THERAPIES

Substantial progress has been made in the treatment of chronic hepatitis B, but quite serious new problems arose after the introduction of nucleoside/nucleotide analogues in clinical practice. The most important of them is the selection of drug-resistant mutations. Drug-resistance usually is accompanied by virologic breakthrough during therapy and increased ALT levels after initial normalization^[35]. In some patients this may cause severe hepatic flare with liver failure and death^[35]. In addition, resistance to one antiviral drug may confer resistance to other agents and may limit future treatment options^[35]. Another important problem is the high rate of relapse after therapy.

With regards to the limited long-term efficacies of the approved therapeutic regimens, therapy should only be recommended if the expected benefit exceeds significantly abstain from treatment^[35]. The choice of therapy should take into account the patient's age, co-morbid medical conditions, the severity of the liver disease and the risk of drug-resistance^[4].

Interferon based therapy is associated with more durable response and the absence of drug-resistant mutations^[42]. However, IFN is effective mainly in a subgroup of young patients with high ALT levels and low viral load^[7,37]. At present it is generally accepted that subjects with normal or slightly elevated ALT (< 2x ULN) are not indicated for antiviral therapy^[8,9]. These patients should be strictly monitored at 3-mo intervals. Low serum HBV DNA levels (HBV DNA < 30 000 000 copies/mL) are an important predictor of response to both conventional IFN and PEG IFN therapy^[37]. With regards to this the initiation of IFN should be avoided in patients with very high viral load and especially if ALT is not markedly elevated. If possible the start of IFN therapy should be postponed for the moment, when serum HBV DNA and ALT levels predict higher likelihood of treatment response. High baseline ALT levels are the most important predictor of

response to lamivudine and adefovir as well^[42]. However, it should be mentioned that the high levels of ALT also are a predictor of spontaneous remission in HBeAg-positive CHB. So the decision to start nucleoside analogue should balance between the benefits of this treatment and the risk of drug resistance and hepatic flare.

Interferon based treatment is also limited by significant disadvantages in terms of injection-based application, poor tolerability, potentially severe side-effects, contraindications and relatively high cost. Flu-like symptoms, fatigue, bone marrow suppression thyroid disorders, irritability and depression are the most common adverse effects^[5]. Patients should be closely monitored with monthly clinical and laboratory examinations. Approximately one-third of subjects may require dose reduction and 5% may discontinue therapy prematurely due to the adverse events.^[5] Furthermore, IFN and PEG IFN are contraindicated in decompensated cirrhosis as well as in subjects with autoimmune disorders. They are also ineffective in immunosuppressed patients. In fact nucleoside or nucleotide analogues are the only available treatment option in decompensated cirrhosis and in immunosuppressed subjects.

TREATMENT GOALS

Sensitive HBV DNA assays revealed that HBV replication might persist even after HBsAg seroconversion and this finding changed our treatment concept. Although the new antiviral agents significantly suppress HBV-replication, there is a pool of covalently closed circular DNA (cccDNA), resistant to the available antiviral treatment. This cccDNA serves as a template for viral transcription, so viral relapses occurs once antiviral medications are discontinued^[4]. At the present level of knowledge it is impossible "to eradicate the virus" The realistic treatment goal now is to achieve durable response by clearance of HBeAg, sustained decrease in serum HBV DNA levels with normalization of ALT, improvement of liver histology and stopping of liver fibrogenesis^[4].

In conclusion the competition between IFN based therapy and nucleoside or nucleotide analogues treatment still remains. IFN can cure the liver disease while nucleotide analogues only suppress the viral replication and can reduce the liver fibrosis. In the future IFN treatment in HBeAg-negative CHB might need to be prolonged for 24-mo or even longer by using maintenance or intermittent treatment course with the lowest effective IFN or PEG IFN doses. Nucleoside/nucleotide analogues are a promising treatment option, but additional data for treatment duration and long-term post-treatment outcome are necessary.

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