The "return" of hepatitis B

Zahariy A Krastev

Zahariy A Krastev, Clinic of Gastroenterology, St. Ivan Rilsky University Hospital, Sofia Medical University, Sofia, Bulgaria. Correspondence to: Zahariy A Krastev, MD, PhD, DSc. Clinic of Gastroenterology, St. Ivan Rilsky University Hospital, 15, Acad. Ivan Geshov Blvd., Sofia 1431, Bulgaria. zahkrastev@yahoo.com Telephone: +359-2-9526319 Fax: +359-2-8510615 Received: 2006-06-27 Accepted: 2006-07-18

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 α2a), 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 HBsAg-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 α2a at doses 90 mcg/wk and 180 mcg/wk in HBsAg-positive patients. These results provide a rational for further clinical trials with lower doses PEG IFN α2a 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 HBsAg, 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 nucleoside 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.

© 2006 The WJG Press. All rights reserved.

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

KrustevZA. The "return" of hepatitis B. World J Gastroenterol 2006; 12(44): 7081-7086

http://www.wjgnet.com/1007-9327/12/7081.asp

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[3].

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[4]. 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. 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 α2a as well as three nucleoside or
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. 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 10^2 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. 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, 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. Subsequently, 6 to 12 mo post therapy HBsAg loss was found only in 8% of HBeAg-positive patients. These treatment doses and durations have been validated as a “standard IFN therapy” for HBeAg-positive CHB by both EASL and AASLD treatment guidelines. 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”. 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 α2a is superior to conventional IFN in HBeAg-positive CHB. In addition no significant difference was found in PEG IFN α2a efficacy given in dose of 90 mcg/wk in comparison to dose of 180 mcg/wk (Table 1).

Having in mind that the majority of the side effects of PEG IFN α2a are dose-related, these results provide a rational for further clinical evaluation of lower dose of PEG IFN α2a 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. 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.

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. Therefore viral suppressive therapy might be continued for 1-10 years for viral elimination. 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. Only the longer IFN course was identified as a significant factor of long-term remission, while the higher actual IFN dose was...
not\[7\]. An Italian study showed a 30% SR after a 24-mo maintenance course with 6 MIU IFN tiw\[18\]. 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, these 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 α2a\[18\]. 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\[18\] provide a rational for further clinical trials with low-dose intermittent PEG INF therapy in responders of 12-mo PEG IFN α2a 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 α2a 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 α2a is with efficacy, similar to that of PEG IFN α2a 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\[33\]. 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 determine 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 virological breakthrough during therapy and increased ALT levels after initial normalization\[36\]. In some patients this may cause severe hepatic flare with liver failure and death\[30\]. In addition, resistance to one antiviral drug may confer resistance to other agents and may limit future treatment options\[36\]. 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 abstin 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\[35\].

Interferon based therapy is associated with more durable response and the absence of drug-resistant mutations\[42\]. However, IFN is effective mainly in a sub-group of young patients with high ALT levels and low viral load\[4,37\]. 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\[32\]. 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\[31\]. 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\[31\]. 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 occur once antiviral medications are discontinued\[39\]. 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\[41\].

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.

**ACKNOWLEDGMENTS**

The author thanks Dr. D Jelev and Dr. K Antonov for their collaboration in the field of hepatitis B research.

**REFERENCES**

1 Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2001; 34: 1225-1241
2 Maddray WC. Hepatitis B: an important public health issue. J Med Virol 2003; 61: 362-366
3 Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006; 43: S173-S181
4 Osborn MK, Lok AS. Antiviral options for the treatment of chronic hepatitis B. Antimicrob Chemother 2006; 57: 1030-1034
5 Conjevaram HS, Lok AS. Management of chronic hepatitis B. J Hepatol 2003; 38 Suppl 1: S90-S103
6 Thomas H, Foster G, Platis D. Mechanisms of action of interferon and nucleoside analogues. J Hepatol 2003; 39 Suppl 1: 693-698
7 Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Ann Intern Med 1993; 119: 312-323
8 EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002: Geneva, Switzerland. Consensus statement (short version). J Hepatol 2003; 38: 533-540
9 Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology 2004; 39: 857-861
10 Reichen J, Bianchi L, Frei PC, Malé PJ, Lavanchy D, Schmid M. Efficacy of steroid withdrawal and low-dose interferon treatment in chronic active hepatitis B. Results of a randomized multicenter trial. Swiss Association for the Study of the Liver. J Hepatol 1994; 20: 168-174
11 Sarin SK, Gupte RC, Varadaraj G, Shih SH, Tappero JW, Albrecht WD, Heathcote EJ. Low-dose interferon alpha-2a in the treatment of chronic hepatitis B. A randomized double-blind placebo-controlled study. J Hepatol 1996; 25: 56-61
12 Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandeep K, Chutaputti A, Zahm FE, Pluck N. Peginterferon alpha-2a (40 kDa): an advance in the treatment of chronic hepatitis B e antigen-negative chronic hepatitis B. J Viral Hepat 2003; 10: 298-305
13 Brunetto MR, Oliveira F, Demartini A, Calvo P, Manzini P, Cerenzia MT, Bonino F. Treatment of interferon with chronic hepatitis B associated with antibody to hepatitis B e antigen. J Hepatol 1991; 13 Suppl 1: S8-S11
14 Krastev Z, Antonov K, Vassilev M, Jelev D. Treatment with low-dose interferon-alpha in Bulgarian HBeAg-negative patients with chronic hepatitis B. J Clin Gastroenterol 1998; 27: 367-368
15 Gupte RC, Thakur V, Malhotra V, Sarin SK. Low-dose recombinant interferon therapy in anti-HBE-positive chronic hepatitis B in Asian Indians. J Gastroenterol Hepatol 1998; 13: 675-679
16 Nowak MA, Bonhoeffer S, Hill AM, Boehme R, Thomas HC, McDade H. Viral dynamics in hepatitis B virus infection. Proc Natl Acad Sci USA 1996; 93: 4298-4302
17 Manesis EK, Hadziyannis SJ. Interferon alpha treatment and retreatment of hepatitis B e antigen-negative chronic hepatitis B. Gastroenterology 2001; 121: 101-109
18 Lam pertico P, Del Ninno E, Viganò M, Romeo R, Donato MF, Sablon E, Morabito A, Colombo M. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. Hepatology 2003; 37: 756-763
19 Krastev Z, Jelev D, Antonov K. Long-term supportive cyclical re-treatment in HBeAg-negative HIf responders. J Hepatol 2005; 42: 277-278
20 Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germaindis G, Yurd彦din C, Diago M, Gurel S, Li MY, Button P, Pluck N. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2005; 353: 1206-1217
21 Marcellin P, Bonino F, Lau G, Farci P, Yurd彦din C, Piratvisuth T, Jin R, Gurel S, Hadziyannis S, Jin R, Lu ZM, Popenescu M. The majority of patients with HBeAg-negative chronic hepatitis B treated with peginterferon alfa-2a (40KD) (Pegassist) sustain responses 2 years post-treatment. J Hepatol 2006; 44 Suppl 2: S274
22 Dienstag JL, Cianciara J, Karayacim S, Kowdle KV, Willems B, Plisec S, Woessner M, Gardner S, Schiff E. Durability of serologic response after lamivudine treatment of chronic hepatitis B. Hepatology 2003; 37: 748-755
23 Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, Condrey LD, Woessner M, Rubin M, Brown NA. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999; 341: 1256-1263
24 Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998; 339: 61-68
25 Guan R, Lai CL, Liaw YF, Lim SG, Lee CM. Efficacy and safety of 5 years of lamivudine treatment of Chinese patients with chronic hepatitis B. J Gastroenterol Hepatol 2001; 16 Suppl 1: A60
26 Rizzetto M, Marzano A, Laggett M. Treatment of hepatitis B e antigen-negative chronic hepatitis B with lamivudine. J Hepatol 2003; 39 Suppl 1: S168-S171
27 Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, Hawley S, Barber J, Condrey L, Gray DF. Efficacy of lamivudine in patients with hepatitis B e antigen-negative hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. Hepatology 1999; 29: 889-896
28 Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology 2002; 36: 219-226
29 Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, Gane E, Fried MW, Chow CW, Paik SW, Chang WY, Berg T, Flisiak R, McClound P, Pluck N. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352: 2682-2695
30 Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosارت CL. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003; 348: 808-816
31 Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosart CL. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med 2003; 348: 800-807
32 Wong SN, Lok AS. Update on viral hepatitis. 2005. Curr Opin Gastroenterol 2006; 22: 241-247
33 Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, Lok AS, Han KH, Goodman R, Zhu J, Cross A, DeHertogh D, Wilber R, Colombo R, Apelian D. A comparison of entecavir and lamivudine for HBV-positive chronic hepatitis B. N Engl J Med 2006; 354: 1001-1010
34 Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colombo R, Fernandez L. Entecavir versus lamivudine for chronic hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med 2006; 354: 1011-1020
35 Lok AS. The maze of treatments for hepatitis B. N Engl J Med 2005; 352: 2743-2746
36 Chang TT, Gish RG, Hadziyannis SJ, Cianciara J, Rizzetto M, Schiff ER, Pastore G, Bacon BR, Poynard T, Joshi S, Klesczechowski KS, Thiry A, Rose RE, Colombo R, Hindes RG. A dose-ranging study of the efficacy and tolerability of entecavir in Lamivudine-therapeutic chronic hepatitis B patients. Gastroenterology 2005; 129: 1198-1209
37 Perrillo RP. Current treatment of chronic hepatitis B: benefits and limitations. Semin Liver Dis 2005; 25 Suppl 1: 20-28
38 Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, Lee SS, Chan S, Shiffman ML, Washington MK, Rigney A, Anderson J, Mondou E, Snow A, Sorbel J, Guan R, Rousseau F. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. Arch Intern Med 2006; 166: 49-56
39 van Boommel F, Wünsche T, Mauss S, Reinke P, Berg A, Schürmann D, Wiedemann B, Berg T. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant
hepatitis B virus infection. Hepatology 2004; 40: 1421-1425

40 Lim SG, Krastev Z, Ng TM, Mechkov G, Kotzev IA, Chan S, Mondou E, Snow A, Sorbel J, Rousseau F. Randomized, double-blind study of entecavir (FTC) plus clevudine versus FTC alone in treatment of chronic hepatitis B. Antimicrob Agents Chemother 2006; 50: 1642-1648

41 Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, Peynard T, Myers M, Chao G, Lloyd D, Brown NA. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005; 129: 528-536

42 Fung SK, Lok AS. Treatment of chronic hepatitis B: who to treat, what to use, and for how long? Clin Gastroenterol Hepatol 2004; 2: 839-848