CURRENT TREATMENT OF CHRONIC HEPATITIS B

Ghodrat Montazeri MD

The primary goal of therapy in patients with chronic hepatitis B is suppression and long-lasting maintenance of hepatitis B virus DNA to its lowest possible level. The threshold of hepatitis B virus DNA level for therapy is $\geq 10^5$ copies/mL for HBeAg-positive patients and $\geq 10^4$ for those with HBeAg-negative chronic hepatitis B. Interferon alpha-2b, lamivudine, and adefovir-dipivoxil are approved by FDA and could all be used as an initial first-line therapy in chronic hepatitis B. Adding lamivudine to either conventional interferon or peg-interferon did not increase the efficacy. Adding lamivudine to adefovir had also no additional effect in compensated patients. Response rate is about 30% – 40% with first-line drugs. Peg-interferon, which recently received the FDA approval, is associated with an increased response rate. Further long-term studies are required to use peg-interferon as a widespread first-line treatment. Treatment strategy is changing towards using prolonged combination therapy with evolving nucleoside analogues with or without an immunomodulatory agent, aiming at eradicating covalently closed circular DNA.

Keywords: Adefovir • chronic hepatitis B, treatment • interferon • lamivudine • nucleocapsid analogue

Disease burden

HBV infection is a global health problem. Worldwide, around two billion people are infected of whom 350 million are suffering from CHB. Long-term sequelae of HBV infection, hepatocellular carcinoma (HCC) and cirrhosis, are responsible for one million deaths per year. The disease burden of HBV varies in different parts of the world. The HBs antigen (Ag) carrier rate is less than 2% in western Europe and North America. South-East Asia, Africa, and the Mediterranean basin are known as high-prevalence areas, where the carrier rate is more than 8%. In the Middle-East, the carrier rate ranges from 2% – 7%. Iran can be considered as an intermediate-prevalence zone. Sofar, several sero-epidemiological studies have been carried out in Iran. Depending on the gender, studied population, place and time of the study, carrier rates have been reported from 1.6% to 7.5%. It was also reported that HBV is still the most common cause of liver cirrhosis in Iran. CHB is the major cause of end-stage liver disease, with 25% of the patients dying prematurely of liver cirrhosis and HCC.

Biology of HBV

HBV, a member of the Hepadnaviridae family,
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is a circular small DNA virus and a partially double-stranded 3.2 kilobase (kb) pair molecule that contains four overlapping reading frames—s, c, x and p. Attachment to the cell membrane is mediated by a pre-s domain surface protein. After attachment into a hepatocyte, it is converted to cccDNA within the nucleus of the hepatocyte by host DNA polymerase.

Replication of HBV is not via the conventional process of semiconservative DNA synthesis. Instead, it involves synthesis of RNA intermediates which is reversely transcribed to minus viral DNA. cccDNA permanently infects hepatocytes and is used as a template for viral replication. Pregenomic RNA is formed from cccDNA by hepatocyte polymerase II and is transported into the cytoplasm. Pregenomic RNA is served as a template for viral replication as well as for the production of both HBcAg and HBV polymerase. It is incorporated into a nucleocapsid and forms a minus strand by viral reverse transcriptase (RNA-dependent DNA polymerase). A single minus strand is completed by the synthesis of a plus strand. Therefore, a relaxed double-stranded DNA is formed inside the nucleocapsid by viral polymerase. Structural viral RNA is produced inside the nucleus and transported into the cytoplasm to make the structural viral proteins (s, x, and e antigen). Nucleocapsids are either enveloped and secreted as Dane particles into the circulation or transported back into the nucleus and changed into cccDNA to maintain the intracellular viral replication.

HBV is classified serologically and genotypeically. According to serologic studies of HBsAg, nine serotypes have been reported: ayw1, ayw2, ayw3, ayw4, ayr, adw2, adw4, adrq+, and adrq−. Based on the S gene alone or the whole genome analysis, eight genotypes have been identified (A to H). The genotype of 26 patients with CHB in Iran was studied. All were classified as type D.

Natural history of HBV infection

Perinatal infection is almost always asymptomatic and evolves to chronicity in 90% of instances. Chronicity is defined as having HBsAg and HBc antibody (Ab) for more than six months. The risk of getting perinatal infection depends on the mother’s DNA level. Infection acquired in early childhood (1 – 5 years of age) is generally asymptomatic and evolves to chronicity in 30% of cases. Infection in adults is usually symptomatic and evolves to chronicity in about 5% of patients.

There are two types of CHB—eAg-positive and eAg-negative. Both types are associated with active HBV replication and could produce active liver disease. HBeAg-positive CHB consists of immunoreactive and immunotolerant phases. The immunoreactive phase is mostly seen in adults, with patients having elevated liver enzymes and high levels of viral DNA. The immunotolerant phase is usually seen in children who are infected at birth. They have normal liver enzymes, despite having very high levels of viral replication. The immunotolerant phase may change into the immunoreactive phase. The latent period may be 20 – 30 years for those who are infected at birth and much shorter for those who have been infected in adolescence or adulthood.

Seroconversion from HBeAg-positive to HBeAg-negative and HBeAb-positive states are followed by biochemical, biological and histological resolution. In most patients, this is a transient phase to the inactive carrier state. The biochemical, virological, and histological abnormalities will persist in 1% – 5% of patients in spite of seroconversion. This group of patients is called HBeAg-negative CHB. HBeAg, CHB is prevalent worldwide but the rate is higher in the Mediterranean basin. These patients have indolent phases and are less replicative, produce more aggressive liver histological changes, and are less responsive to therapy.

Treatment

Interferon, lamivudine, adefovir-dipivoxil, entecavir, and peglated-interferon have received FDA approval for the treatment of CHB in 1991, 1998, 2002, April 2005, and May 2005, respectively. Among these, interferon, lamivudine and adefovir-dipivoxil could be used as the first-line therapy for patients with either eAg-positive or eAg-negative CHB. Interferon has no direct antiviral effect but can induce expressions of different antiviral genes. It increases cellular immune response against hepatocytes infected with HBV by increasing class-I HLA antigen. Interferon also stimulates T helper cells and natural killer T lymphocytes. Lamivudine is a negative enantiomer of 2, 3, dideoxy-thiacytidine, and is a competitive inhibitor of cytosine. It is an inhibitor of reverse transcriptase and blocks elongation of
both minus and plus DNA strands. Being a negative enantiomer explains the good safety profile of lamivudine. Adefovir-dipivoxil (9-(2-phosphonyl-methoxyethyl)-adenine) is incorporated into the growing DNA and prevents further growth of the strand. Adefovir-dipivoxil (9-(2-phosphonyl-methoxyethyl)-adenine) is incorporated into the growing DNA and prevents further growth of the strand. Because the nature of the disease and response to therapy are different in HBeAg-positive and HBeAg-negative patients, responses to the therapy are discussed separately.

1) eAg-positive CHB
   a) Interferon: A meta-analysis from 15 controlled randomized trials, involving 837 adult cases of eAg-positive CHB, showed that interferon was an effective drug. HBsAg loss was 7.8% (vs. 1.8% in the control), eAg loss was 32% (vs. 12% in the control), and loss of HBH DNA was 37% (vs. 17% in the control). Low HBV DNA and high alanine aminotransferase (ALT) levels were the best predictors for good response. Such a dramatic response was not seen in Asian patients. The effect of interferon was analyzed in a recent meta-analysis, involving 1,299 patients and 444 controls in 24 randomized control trials, with a mean follow-up of 6.1 years. It was concluded that interferon significantly improves HBsAg loss, increases seroconversion, and produces sustained normalization of liver enzymes, when compared to controls. True long-term benefits of interferon were studied in 165 patients who had received interferon and were followed for a mean of 8.8 years. This work clearly showed that interferon increases survival and reduces the risk of HCC. In another long-term study, 103 cases were treated and followed for a mean of 6.2 years. The responders and non-responders were compared. It was shown that interferon could prevent cirrhosis.

   b) Lamivudine: One-hundred mg daily lamivudine for one year results in sustained suppression of HBV DNA, eAg loss, normalization of liver enzymes, and improvement of liver histology. The response is increased by extending the duration of therapy. Seroconversion increases from 17% at one year to 27%, 40%, 47%, and 50% at 2, 3, 4, and 5 years, respectively. Seroconversion increased to 56% in patients with ALT levels more than five times the upper limit of normal. The major drawback in lamivudine therapy is the development of YMDD mutants, which is increased from 14% – 32% at one year to 69% at five years. Lamivudine has been used in HBV-infected immunocompromised hosts. In this respect, lamivudine has been used in 14 Iranian renal allograft recipients, of whom three were eAg-positive and 11 were eAg-negative. It produced HBV DNA suppression and liver enzyme normalization plus seroconversion in all patients. Limitations of this study were the small sample size studied and the lack of a control group.

   c) Adefovir-dipivoxil: Ten mg daily adefovir for one year results in sustained viral suppression, improved histological response and normalization of ALT. By extending therapy, the response is further improved. At week 72, eAg is lost in 44% of patients, liver enzyme normalized in 75% of patients, and seroconversion occurred in 23% of patients. HBV DNA was undetectable by polymerase chain reaction (PCR) in 46% of patients while they were receiving treatment. No mutant was reported by one year of therapy. Mutation by week 144 at two novel sites, rtA181V and rtN236T of polymerase gene was seen. The estimated rate of mutation is 4% at three years of therapy.

   d) Peg-interferon: Forty KD peg-interferon was compared with conventional interferon in 194 patients. It was shown that peg-interferon is superior to conventional interferon regarding eAg loss, HBV DNA suppression, and ALT normalization. Combined end-point response including eAg loss, normalization of ALT and suppression of HBV DNA, altogether, was 24% in peg-interferon as compared to 12% in the conventional interferon group.

   e) Combination therapy: Conventional interferon used in combination with lamivudine. Additive effects were reported, however in general, the results are conflicting. Peg-interferon was used alone and in combination with lamivudine for treatment of 307 patients. The loss of eAg was 36% in the peg-interferon group. The response rate to peg-interferon therapy was more than that for lamivudine and conventional interferon therapy. The addition of lamivudine did not increase the response rate. We compared lamivudine alone and in combination with interferon in interferon-
non-responder patients. Combination therapy using interferon and lamivudine had the same response rate as that for lamivudine monotherapy. Adefovir was used in combination with lamivudine. In another study, 59 eAg-positive patients resistant to lamivudine were investigated. There was no significant difference between the combination group and that of adefovir monotherapy in terms of DNA suppression (-3.59 and -4.04 log copies/mL), normalization of ALT (53% and 47%), and HBeAg loss (3 patients in each group). In another study, adefovir alone and in combination with lamivudine was used for therapy of 112 treatment-naive patients. There were no significant differences between adefovir-lamivudine and adefovir monotherapy in terms of HBV DNA suppression (-5.41 and -4.8 log copies/mL), ALT normalization (39% and 41%), and eAg loss (19% and 20%). Resistance was 2% in the combination group vs. 20% in the lamivudine group ($P < 0.003$).

2) eAg-negative CHB

a) Interferon: Sustained virological response with interferon is 15%–25%. Durability of the response was increased in patients who had received interferon for more than 12 months; 32% of responders lost the HBsAg by that time. Long-term complications are lower in responders than non-responders. In general, it is shown that with the same dose and duration of treatment, the response rate in HBeAg-negative patients with CHB is lower than that in HBeAg-positive patients. This is partly compensated by increasing the duration of therapy to one year. In addition, the long-term prognosis of responders is better than non-responders in patients with eAg-negative CHB.

b) Lamivudine: Two-thirds of patients respond at the end of 12 months of treatment as measured by therapy end-points including biochemical, virological, and histological indicators; the relapse rate was however, high. Longer duration of therapy can maintain virological and biochemical responses, but the emergence of YMDD mutation is a major drawback. In general, 40% of patients will maintain normal liver enzymes and undetectable DNA, if they receive lamivudine for more than 30 months. The incidence of YMDD increases by time from 19% – 27% at one year to 44%, and 60% at 2, and 4 years, respectively. The biology of the YMDD mutant is different in eAg-negative variants; it can cause a more progressive liver disease than its eAg-positive counterparts.

c) Adefovir: In a randomized double-blind clinical trial, 185 patients used 10 mg adefovir daily for 48 weeks. Patients who had received adefovir improved significantly as compared to the placebo group in terms of histological (64% vs. 33%), virological (-3.4 log vs. -1.35 log DNA copies/mL), and biochemical response (72% vs. 29%). It was shown that the 48 weeks beneficial effect of adefovir will be maintained at 144 weeks if the drug is continued. The benefits which were achieved at 48 weeks will be lost, if the drug is discontinued. The resistance rate was 5.9% and occurred at two different loci of the polymerase gene—rtN236T and rtA181V.

d) Combination therapy: Lamivudine was used alone and in combination with peg-interferon for 48 weeks in several double-blind trials. In this study, 177 patients received 180 µg peg-interferon weekly plus placebo; 179 patients received 180 µg peg-interferon weekly plus 100 mg lamivudine daily; and 181 patients received 100 mg lamivudine daily alone. Sustained virological and biochemical responses were significantly higher in peg-interferon group as compared to the lamivudine group. The addition of lamivudine had no additive beneficial effect. We compared the beneficial effect of lamivudine alone and in combination with conventional interferon therapy in 38 patients who did not respond previously to interferon. Twenty-two patients were eAg-negative and the rest were eAg-positive. The response rates of group 1 (lamivudine alone) and group 2 (lamivudine + interferon) were not significantly different in terms of histological (38.8% vs. 27.7%) and biochemical responses (31.2% vs. 28.06%). It was concluded that lamivudine could be a therapeutic choice for those who were resistant to interferon and that the addition of conventional interferon to lamivudine could not increase the response rate. In another study conducted in Iran, a combination of lamivudine and interferon was studied in 22 patients with CHB who had no response to one year of lamivudine monotherapy. In this study, the combination therapy of lamivudine and interferon appeared to be superior to lamivudine monotherapy. However, clear-cut conclusions could not be drawn from this
work because of its small sample size in each subgroup and its ill-defined end-points.64

e) Decompensated cirrhosis: Conventional interferon therapy is prohibited for this condition. Lamivudine can suppress viral replication. Liver functions are improved and liver transplantation becomes less urgent and thus can be postponed.65 However, the emergence of antiviral emergence could be fatal in some cases. In addition, the beneficial therapeutic effect of using antiviral agents in patients with an HBV DNA concentration of < 10^5 copies/mL is still unclear.66 Lamivudine was used in 55 patients with decompensated cirrhosis. Patients had received at least 6 months of lamivudine therapy. Liver function tests improved. Child-Pugh scores decreased significantly as compared with the baseline values. In addition, four of 22 eAg-positive patients had seroconversion.67 In another study, three patients with cirrhosis were reversed through the treatment. The mean fibrosis score decreased from 5.8 to 0.5. The mean inflammation scores decreased from 10.8 to 3.2, and the mean Child-Pugh scores decreased from 8 to 5.68 The duration of therapy has not been defined in decompensated cirrhosis and long-term beneficial effects of lamivudine on survival have not been delineated. We have to individualize and consider the risks and benefits of long-term therapy in each case.

New nucleoside analogues

a) Emtricitabine (FTC): It is a pyrimidine nucleoside analogue and differs from lamivudine in a fluorine at position 5 of dideoxy ribose. In a study, 25, 100, and 200 mg of emtricitabine were administered to 98 patients (77 eAg-positive and 21 eAg-negative) for 48 weeks. Daily administration of 200 mg continued for another 48 weeks. At the end of the treatment, HBV DNA dropped to ≤4700 copies/mL. Thirty-three percent of patients seroconverted and 85% obtained a normal ALT level. The rate of mutation was 16%, 12%, and 9% for 25, 100, and 200 mg, respectively, after one year of therapy. The mutation was located at the polymerase gene, rtM204 I/T with or without rtL180M and rtV173L. In this study, 200 mg of daily emtricitabine was chosen as an optimal dose with a good safety profile. The role of this drug as monotherapy is, nonetheless limited due to its structural similarity to lamivudine and the risk of resistance development.69

b) Entecavir: It is a cyclopentyle guanosine analogue. It inhibits priming and elongation of viral DNA for both plus and minus strands.70 Therefore, it is superior to lamivudine for the suppression of HBV DNA.71 This drug was used in woodchucks for three years. Survival increased in animals treated for a prolonged time as compared to historical controls. In 8 of 9 animals cccDNA was not detectable in liver samples that were taken at the end of the treatment and remained negative for at least 5 months after cessation of treatment.72 In one study, 709 patients were randomized either to receive lamivudine or entecavir. It was shown that entecavir was superior to lamivudine in terms of virological and histological responses.73 In another study, mutation at positions rt184, rt202, and rt250, were seen in 5.8% of 172 patient who had received lamivudine previously. No mutation was observed in the 432 cases who were not exposed to lamivudine before.74

c) Clevudine: It is a pyrimidine analogue (L-F MAU) which works by inhibiting synthesis of the positive DNA strand.75 In an animal model, it could decrease DNA by 8 log_{10} after 4 weeks of therapy. It could also reduce HBsAg and cccDNA. Of the animals receiving this medication, 50% had no rebound 12 weeks after stopping the therapy.76 Resistance occurred in the animal model in domain B of the polymerase gene by 6 – 12 months of treatment, which can also confer resistance to lamivudine and famcycovir.77 In phase II clinical trials, it had a profound reduction in DNA level by 5 log_{10} after 4 weeks of treatment.78

d) Telbivudine: It is the beta-L configuration of deoxythymidine (Ldt). In one study, 104 HBsAg-positive cases were randomized to receive 400 or 600 mg telbivudine either alone or in combination with lamivudine for 52 weeks. Telbivudine had a higher DNA suppression and HBsAg loss as compared with lamivudine. DNA reduction was -6.01 log, -5.99 log, and -4.57 log; eAg losses were 33%, 17%, and 28%; and the percentages of undetectable DNA were 61% (telbivudine alone), 49% (combination of telbivudine + lamivudine), and 32% (lamivudine alone). YMDD mutants emerged in 4.4% (telbivudine alone), 12.2% (telbivudine + lamivudine), and 12.1% (lamivudine alone) of patients. This study clearly shows that telbivudine is superior to lamivudine and that adding these two drugs had no significant effect. In addition, resistance to
telbivudine is lower than to lamivudine. The safety profile of telbivudine was similar to the placebo.79

Immunotherapy
HBV is not a cytolytic virus. Hepatocyte destruction in CHB is immune-mediated. This is performed by collaboration of immunoreactive T cells and HLA class-I. It is possible to prevent viral entry by stimulating humoral immunity and eradicating infected cells through stimulating cellular immunity.80, 81 In vivo processing of an antigen will engage both humoral and cellular immunity at the same time.82 Although immunotherapy is still in its infancy, it is a promising scientific approach to treat CHB. Different antigens have been used either with or without interferon and nucleoside analogues. In some studies, plasmids of appropriate genes were used to provide constant antigenemia and long-term immune activation.83, 84 Although, the results are conflicting, in general, it appears that cellular and humoral immunity could be stimulated and HBsAg loss was facilitated by immunotherapy. We injected conventional HBsAg intradermally to stimulate the immune system. The intradermal route is preferred because the skin has numerous antigen-presenting cells that exceed 100 times of those in muscles. Forty-two inactive carriers were studied. Twenty µg of HBsAg were injected intradermally at 0, 1, and 6 months. Patients were re-evaluated 6 months after the last injection. The rate of HBsAg loss was 4.47%, which was statistically significant when compared to historical controls.85

YMDD mutants
Drug resistance has not been described with interferon therapy. Lamivudine therapy has been associated with an increased rate of YMDD mutations, of 14% – 32%, at the end of one year, and 69%, at the end of 5 years.40, 44 The most important mutation is the substitution of valine or isoleucine for methionine in the YMDD motif of the HBV polymerase gene (rtM204V/I). In some patients, it is also associated with a second mutation in which methionine is substituted for leucine in an upstream region of the polymerase gene (rtL180M). The emergence of lamivudine resistance is associated with an increase in DNA levels, which will be followed by increase in serum aminotransferases. Administration of adefovir-dipivoxil 10 mg/day is recommended for these patients. Using adefovir alone or in combination with lamivudine has the same result in terms of DNA suppression, rate of eAg seroconversion, and ALT normalization. Switching from lamivudine to adefovir is associated with mild increase in ALT levels. No patient experienced clinically significant ALT level elevations. Therefore, using adefovir alone is adequate in compensated cases.53 However, return of the wild type in the process of switching might be potentially hazardous in decompensated patients; thereby, the addition of adefovir to continued lamivudine therapy is recommended.88

Conclusive remarks and future prospective
Details of an algorithm for the management of CHB were reviewed and updated by experts elsewhere.86 – 90 Here, I try to draw the attention of the readers to the points which are more relevant to our local problems. Interferon, lamivudine, and adefovir-dipivoxil are the three FDA-approved drugs for the first-line therapy for CHB. In choosing which drug to use as the first-line therapy, several factors should be considered. Careful attention should be paid to the long-term efficacy, safety, cost, and patients’ and providers’ preferences. Interferon is an old drug with proven short- and long-term efficacy in the treatment of patients with CHB. It has lots of complications, could not be used in decompensated cirrhosis, and has low efficacy in patients with high viral load and in eAg-negative patients with CHB. On the other hand, it is an immunomodulatory agent and the response is sustained for a longer period as compared with nucleoside analogues.

One year of lamivudine therapy is preferred to 6 months of interferon therapy in western countries from an economic standpoint. It is used orally and has an excellent safety profile. Prolonged lamivudine therapy provides higher and sustained seroconversion and could be used in the treatment of patients with decompensated cirrhosis. Using lamivudine in the treatment of CHB has two major drawbacks: YMDD mutation emerges progressively in prolonged therapy and there is a high relapse rate when therapy is discontinued. The exact biology of YMDD is still not clear. Therefore, unlimited use of lamivudine is not recommended. Sustained eAg seroconversion is achieved by using lamivudine for more than 6 months after the initiation of eAg loss and subsequent eAb production. The duration of
lamivudine therapy to achieve a sustained viral suppression has not been defined in patients with eAg-negative CHB; however, a minimum of 2 years of therapy is recommended.

Adefovir-dipivoxil is a new drug. The emergence of resistance is substantial after 2 years of therapy and viral replication returns when medication is discontinued. There is no cross-resistance between lamivudine and adefovir. Therefore, it is a good choice for patients who are YMDD mutants. It has a good safety profile with a 10 mg daily dose, but it might produce renal failure when higher doses are administered.

Peg-interferon, which recently approved by FDA, appears to be superior to conventional interferon and lamivudine. Adding lamivudine to either conventional or peg-interferon did not increase its efficacy as compared with monotherapy. It is more expensive, has less side effects, and is more efficient as compared to the conventional type. This is not recommended as the first-line therapy either alone or in combination with nucleoside analogues.

Decision to treat is based on viral load and ALT level. DNA levels ≥ 10^{5} in eAg-positive cases and ≥ 10^{4} in eAg-negative patients are the threshold to consider treatment in the presence of elevated ALT. Therefore, we should not pay any attention to the positive qualitative results on PCR. Level of DNA should be quantified using a reliable method. Quantification of DNA is not simple. It requires expertise, reliable kits, and expensive instruments. Physicians who order this test should be aware of all of these limitations. The role of liver biopsy has not been clearly defined in the medical literature. Because of its complications, most investigators and patients are reluctant to perform this procedure. However, its importance should not be underestimated. Regardless of its shortcomings, it is still the gold-standard for evaluation of the degree of liver inflammation and fibrosis. We have shown that 54% of 48 patients who have had constant normal enzymes for 6 months or more, had histology activity indexes of more than 4.\textsuperscript{91} Therefore, normal liver enzymes are not indicative of silent liver damage. On the other hand, clinical trials of emerging new drugs will require closer follow-up of the patients under study. Feasibility and usefulness of frequent liver biopsies under such circumstances are questionable. In such situations, fibrosis markers might help to decrease the need for frequent liver biopsies. Many fibrosis markers, either single or in combination, have been reported. We found that serum hyaluronate at the cutoff point of 126.4 ng/mL could discriminate an extensive fibrosis from a milder form of the disease with a sensitivity of 90.9% and a specificity of 98.1%. Using the same cutoff value, it could discriminate extensive inflammation from its milder counterparts with a sensitivity of 63.6% and a specificity of 92.6%.\textsuperscript{92} Further studies are needed to make this a routine laboratory test.

Biovudine (imported lamivudine) and homemade interferon alpha-2b (PDferon) are available and supported by insurance companies in Iran. Data from double-blind controlled randomized clinical trials are not available to compare the efficacy of biovudine and PDferon with their equivalent international counterparts.

Treatment of CHB is still a far from realized goal. The ultimate goal of therapy is to eradicate cccDNA in hepatocytes. Two theoretical approaches should come to action in the future:

Combination therapy with nucleoside analogues and immunomodulatory agents. With this approach, HBV DNA will be transiently suppressed by the nucleoside analogue and the stimulation of immunity by an immunomodulatory agent could eradicate the viral template completely.

Another means to eradicate the virus is to use combination of nucleoside analogues. Selected nucleosides should not produce cross-reactive mutants and should have the capability to eradicate cccDNA. This approach is similar to what has happened in the treatment of AIDS. It was started with a noneffective monotherapy and evolved into effective multiple drug therapy with time. It appears that for the treatment of CHB, we are living in an era like that of the past, when AIDS was treated ineffectively using a single nucleoside analogue.

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