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<th>Updates in the treatment of chronic hepatitis B</th>
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Background

Approximately 400 million people worldwide are infected with chronic hepatitis B (CHB), with approximately 1 million deaths annually from hepatitis B virus (HBV)-related cirrhosis and hepatocellular carcinoma (HCC). The majority of Asian patients acquire HBV either at birth, or within the first few years after birth, and is characterised by a prolonged immunotolerant phase followed by a prolonged phase of immunoclearance. Patients will undergo hepatitis B e-antigen (HBeAg) seroconversion with development of antibodies to HBeAg (anti-HBe) during the natural evolution of the disease, median age of HBeAg seroconversion being around 35 years. However there may be ongoing disease progression to cirrhosis and HCC after HBeAg seroconversion in a proportion of patients.

Goals of Therapy

The ideal goal of CHB therapy is the complete eradication of HBV, which is not possible with the current available treatment. Even loss of the hepatitis B surface antigen (HBsAg) does not denote complete viral clearance. Hence, short-term goals include normalisation of serum alanine aminotransferase (ALT) levels, HBV DNA suppression, HBeAg seroconversion, and improvement in liver histology, with the aim of achieving the long-term goals of preventing liver cirrhosis, liver failure, and HCC.

Treatment Choices

There are six antiviral agents currently available for the treatment of CHB: lamivudine, adefovir, entecavir, telbivudine, interferon (IFN)-α, and pegylated IFN (peg-IFN). Treatment choice should take into account several important factors of the agent in question, namely antiviral efficacy, drug resistance profile, long-term safety profile, methods of administration, and cost-effectiveness.

IFN-α and pegylated IFN

Standard IFN-α has been shown to be effective in the treatment of CHB. However, peg-IFN has largely surpassed standard IFN in CHB treatment. In one report using suboptimal dose of standard IFN-α, peg-IFN is superior to standard IFN in HBeAg clearance, HBV DNA suppression and normalisation of ALT. Recent studies have focused on combination or sequential therapy with lamivudine. Most studies have not shown any additional benefit of combining one year lamivudine treatment to IFN therapy when assessed at 6 months after stopping of therapies. Although no additional antiviral efficacy is observed, there is evidence that the combination of IFN and lamivudine therapy decreases the development of lamivudine-resistant mutations. (The limiting of lamivudine treatment to only one year in these studies is contrary to most current clinical practice with nucleoside analogues).

In addition, the long-term effectiveness of standard IFN has not been consistently shown. Long term benefits including preventing cirrhosis and HCC were not observed in earlier studies of Japanese and Chinese patients. In a more recent retrospective study of Taiwanese patients with high ALT levels at baseline, IFN was shown to reduce HCC and cirrhosis in HBeAg-positive patients compared to untreated controls. Further results regarding peg-IFN with long off-treatment follow-up is needed to determine its long-term efficacy.

Lamivudine

Lamivudine is the first oral antiviral drug approved for the treatment of CHB, and is effective in reducing the complications of cirrhosis, including decompensation and HCC, in both cirrhotic and pre-cirrhotic patients. Lamivudine is associated with high rates of viral resistance, with a resistance rate of 76% after 8 years of treatment. The initial benefits conferred by lamivudine are reduced in patients who develop lamivudine-resistant mutations during long-term follow-up. However, even among those with drug resistance, the outcome remains better than for untreated patients. Both adefovir and entecavir are effective against lamivudine-resistant CHB, and either can be used.

Adefovir

Adefovir dipivoxil has been shown to be effective in both HBeAg-positive and HBeAg-negative CHB, as well as lamivudine-resistant HBV, with proven long-term efficacy. However, with newer and more potent antiviral agents now available, the main role of adefovir is in patients who have developed resistance to lamivudine or telbivudine. Some studies have shown that adefovir monotherapy in lamivudine-resistant patients is as effective for suppressing HBV DNA as combination therapy with lamivudine, while other studies have shown substantially lower rate of resistance to adefovir when treatment is continued in
combination with lamivudine. We recommend the addition of adefovir for lamivudine-resistant patients as soon as genotypic resistance is detected. Adefovir-resistant HBV is sensitive to both entecavir and lamivudine.

**Entecavir**

Entecavir is the third oral antiviral agent approved for CHB treatment, and is superior to lamivudine. Furthermore, no virological breakthrough from entecavir resistance has been observed after 2 years of treatment in treatment-naive HBeAg-positive patients. The resistance rate in treatment-naive patients is only 1.2% in 5 years. Entecavir has been shown to be effective against lamivudine-resistant HBV at the higher daily dose of 1 mg instead of the recommended 0.5 mg daily dose for treatment-naive patients. However, in patients with pre-existing lamivudine-resistant mutations, there is a lower viral response rate, and the higher rate of developing entecavir resistance. The reason for the higher rate of resistance is because the mutations that characterise lamivudine resistance predispose patients to develop subsequent resistance to entecavir. Therefore, entecavir switching therapy may be less optimal than adefovir add-on therapy for CHB associated with lamivudine resistance.

**Telbivudine**

Telbivudine has been shown to be more potent than lamivudine and adefovir against HBV. However, telbivudine is still associated with higher resistance rates than adefovir or entecavir. Resistance to telbivudine occurs at the same mutation site responsible for resistance to lamivudine; therefore neither is essentially effective for one another once resistance develops. The rate of genotypic resistance after 2 years of telbivudine treatment is 22% and 8.6% among HBeAg-positive and HBeAg-negative patients, respectively.

**Viral Resistance**

The resistance rates of different antiviral agents are shown in figure 1. Development of drug resistance remains a major issue as the majority of CHB patients will require long-term therapy. Flares of hepatitis, liver decompensation and death have been reported to occur in patients who develop viral resistance.

The development of drug resistance also affects further treatment options. Patients who developed lamivudine resistant mutations will have a higher rate of developing subsequent adefovir resistant mutations compared to those patients without lamivudine resistant mutations. Likewise, as described previously, patients who have lamivudine-resistant HBV will also have a higher rate of developing subsequent entecavir resistance.

Given the adverse impact of drug-resistant HBV on the clinical outcome and on subsequent antiviral therapy, the risk of developing resistance should be considered prior to starting antiviral therapy. With the availability of newer and more potent antiviral drugs, the high resistance rate associated with lamivudine limits its use as a first-line agent. However, lamivudine remains the least expensive oral antiviral agent with the longest and largest profile of safety data. Use of the roadmap concept, as outlined later, may identify those patients who will respond more favourably in the long term.

**Treatment Endpoints:**

As complete eradication of HBV is currently not possible with available therapy, various endpoints have been adopted as surrogate markers of successful treatment. These include HBeAg seroconversion, normalisation of ALT, and HBV DNA suppression.

**HBeAg seroconversion**

Traditionally, HBeAg seroconversion has been used as a marker of treatment success, and is included in various treatment guidelines. Those patients who have undergone HBeAg seroconversion are termed "healthy carriers", with low HBV DNA levels, normal ALT, and resolution of necro-inflammatory activity within the liver. However, recent studies have shown that over 70% of CHB patients are HBeAg-negative at the time of developing HCC.

As disease progression still occurs after HBeAg seroconversion in patients who acquire the disease at birth or during early childhood, HBeAg seroconversion should therefore be considered as part of the natural history/progression of CHB infection, and should be taken as a treatment endpoint only in conjunction with other criteria, specifically the HBV DNA and ALT levels.

**HBV DNA levels**

Serum HBV DNA levels have been shown to be important in both the development of liver cirrhosis and for development of HCC. Higher levels of HBV DNA are associated with the development of HCC independent of the HBeAg status and ALT levels. There is no current level of HBV DNA which is considered 'safe' from disease progression or from development of HCC. A cut-off level of >2000 IU/mL was shown to be a strong risk predictor of HCC independent of HBeAg status, serum ALT and underlying cirrhosis. However, even lower HBV DNA levels have been associated with the development of HCC. Given the absence of a 'safe' lower limit for disease non-progression, the optimal treatment goal should therefore be to suppress HBV DNA to the lowest possible level, that is, non-detectability by PCR assays.

**ALT levels**

In Asian CHB patients, it has been shown that patients with ALT levels below half the upper limit of normal (ULN) have the lowest risk of complications compared to those with 0.5 x ULN to 2 x ULN.

Patients who have undergone HBeAg seroconversion with subsequent normal ALT have been traditionally regarded as "healthy carriers" with no or minimal disease progression. However, even in patients with normal ALT after HBeAg seroconversion, the cumulative probability of developing cirrhosis after 17 years was 13%. A recent study of CHB patients showed that 37% of those with persistently normal ALT had significant fibrosis or inflammation on liver.
In the light of these recent studies, the cut-off for the upper limit of normal for ALT is most likely to be lower than the values that are currently used. Even patients with ALT in the upper range of the currently accepted normal range are at risk of developing cirrhosis. Ongoing disease monitoring with consideration of antiviral therapy should be given for patients with significant degree of liver fibrosis. Furthermore, treating only those patients with ALT >2 x ULN, as indicated by most current guidelines, would exclude a significant proportion of patients (patients with ALT 0.5 - 2 x ULN) who would benefit most from antiviral therapy because of the higher risk of having or developing significant liver disease in these patients.

**Candidates for Therapy**

In HBeAg-positive patients, the ideal candidates for treatment would be those with a prolonged phase of immune-clearance. Immunotolerant patients, that is, young patients with normal ALT levels, can be monitored and treatment may not be required until active hepatitis occurs during the onset of loss of immunotolerance. Unfortunately, there are as yet no specific criteria to define or identify the time at which immunotolerance ends and immune clearance starts. An elevated ALT level is used as a surrogate marker of inflammation and histological activity, and as a marker for loss of immunotolerance. Whether this is an adequate marker remains to be determined. Nonetheless, it seems reasonable that patients with ALT levels between 1 - 2 X ULN should probably be treated. In patients with evidence of cirrhosis and HBV DNA >2000 IU/mL, they should receive antiviral treatment regardless of the ALT levels.

A significant proportion of patients who become HBeAg-negative with positive anti-HBe will have elevated HBV DNA levels. Although the median HBV DNA levels are lower than for HBeAg-positive patients, these patients tend to be older and have more advanced underlying liver disease. In the current AASLD guidelines, indications for treatment include patients with ALT>2 x ULN and HBV DNA levels ≥20,000 IU/mL, and no treatment for those with ALT <1 x ULN irrespective of HBV DNA levels. This would exclude a substantial amount of patients who would be at high risk of disease progression, including patients who already have cirrhosis. In an alternative treatment algorithm, indications for treatment included ALT >1 x ULN and HBV DNA >2,000 IU/mL, whereas those with HBV DNA <2000 IU/mL and normal ALT would not be treated. Both guidelines suggest liver biopsy to determine disease activity and stage of fibrosis in patients who have ALT and HBV DNA levels in the range outside the definite treatment or within the non-treatment levels. The summary of the AASLD guidelines and the alternative treatment algorithm is shown in figure 2 and 3 respectively. The arguments against the current AASLD treatment guidelines have been summarised in a recent review article.

**Duration of Therapy**

Given the lack of a clearly defined endpoint in the treatment of CHB, the duration of therapy is likewise not clearly defined. The long-term goals of preventing cirrhosis and the development of HCC are likely to be achieved by prolonged suppression of HBV replication. In HBeAg-positive patients, the current AASLD guidelines suggest stopping treatment 6 months after HBeAg seroconversion (regardless of HBV DNA or the ALT levels), and re-treat if relapse should occur. An alternative treatment algorithm suggests that treatment can be stopped 6-12 months after HBeAg seroconversion, providing HBV DNA is undetectable by PCR. The latter approach would seem more appropriate given the inadequacy of HBeAg seroconversion alone as a treatment endpoint, and also the high rate of relapse after discontinuation of therapy. Close monitoring of patients after stopping therapy is mandatory. We would recommend checking the HBV DNA levels 1 month after stopping therapy, and 3 monthly thereafter. Antiviral therapy should be restarted in those with evidence of reactivation. For HBeAg-negative patients, both guidelines suggest that long-term therapy is required.

Long-term antiviral therapy raises the concern about the development of drug-resistant mutations. Despite this, patients will still benefit from antiviral therapy even with the occurrence of drug-resistant mutations. In patients treated with prolonged lamivudine therapy, patients with drug-resistant HBV still benefit from treatment when compared to patients with no treatment. With newer and more potent antiviral drugs with higher genetic barrier, such as entecavir, resistance is likely to become a lesser problem.

Prolonged antiviral therapy also raises the concern about drug toxicity. Older agents, such as lamivudine and adefovir, have established long-term safety data, whereas newer agents are currently lacking in long-term data both for efficacy and safety. Despite this, long-term drug toxicity with long-term therapy is an unlikely problem given the preclinical safety results of the currently licensed nucleotide/nucleotide analogues. In general, all the available oral nucleoside analogs are well tolerated. The documented nephrotoxic effect of adefovir occurs rarely at the dose used for HBV treatment, although renal function should be monitored regularly whilst patients remain on treatment.

The advantage of interferon-based therapy over oral antiviral therapy is that the duration of therapy is more clearly defined. However, the optimal length of interferon therapy remains to be determined. The advantage of a defined treatment length is offset by its side effects and the high proportion of patients who will not respond to IFN therapy and will require further therapy with oral nucleoside analogs. Even in patients with IFN-associated HBeAg seroconversion, long-term monitoring of HBV DNA levels should be performed.

**Monitoring Therapy**

None of the published guidelines provide specific
criteria for on-treatment monitoring of patients. During antiviral therapy, the degree of viral suppression has been shown to be the most important determinant of therapeutic outcomes. More specifically, the importance of effective early viral suppression in determining long term treatment outcome has been shown in several studies using lamivudine, adefovir, peg-IFN-α-2a, and telbivudine. A more recent study of lamivudine treatment has shown that HBV DNA levels of less than 2,000 IU/mL as early as week 4 can be used to predict accurately HBeAg seroconversion with ALT normalisation and HBV DNA levels <2000 IU/mL without emergence of lamivudine-resistant mutations, at year 5.

The use of early monitoring of viral suppression is the mainstay of the recently published roadmap concept, as shown in figure 4. Assessment at week 12 and 24 for primary non-response and early predictors of efficacy respectively should be used to guide subsequent treatment choices. The roadmap concept is useful when initiating therapy with a drug with higher rates of resistance or lower antiviral potency, and maybe potentially useful in patients with pre-existing drug-resistant mutations. Recent evidence showed that early viral suppression with adefovir in treating lamivudine-resistant HBV was associated with more favourable outcomes.

Conclusions

The treatment paradigm is continuing to evolve with better understanding of the natural history of HBV infection. Currently, long-term suppression of HBV replication should be the primary aim. Although peg-IFN therapy offers a finite duration of therapy, the long-term outcomes remain to be fully determined. In addition, only patients with high ALT levels are suitable, and a high proportion of patients have a suboptimal response in terms of HBV DNA suppression. Although long-term benefits are established for oral nucleoside/nucleotide analogues, the benefits of treatment are reduced with the development of drug-resistant mutations.

The optimal choice of the antiviral agent in treatment-naive patients should be a drug with high antiviral potency coupled with a high genetic barrier to reduce the risk of resistance. Entecavir is a significant improvement in the current antiviral strategy, achieving both sustained viral suppression with minimal risk of drug resistance. If a drug with lower genetic barrier is used, identifying early factors such as viral load to predict long-term outcome is important. This would select out patients most likely to achieve successful long-term viral suppression with their current regimens, and an alternative agent can be offered to those with suboptimal early viral response.
References