

# Management of chronic hepatitis B

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## 1. Introduction

Hepatitis B virus (HBV) infection is a global public health problem [1]. It is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. It is estimated there are at least 400 million HBV carriers in the world and that up to one million die annually due to hepatitis B associated liver disease. Efforts to prevent infection are critical in the global eradication of hepatitis B. Improvement in treatment options will reduce morbidity and mortality for some individuals who are chronically infected, but current treatment has limited long-term efficacy. Thus, a careful understanding of the natural history of chronic HBV infection, factors affecting disease progression, and benefits and risks of various therapies is important in the management of patients with chronic hepatitis B.

## 2. Natural history

The natural course of HBV infection is determined by the interplay between virus replication and host immune response. The long-term outcome of chronic HBV infection depends on the severity of liver disease at the time when virus replication is permanently suppressed. Chronic hepatitis B infection consists of four phases [2]. The first phase of chronic HBV infection acquired during childhood or adulthood and the second phase of perinatally acquired HBV infection are characterized by the presence of hepatitis B e antigen (HBeAg) and high serum levels of HBV DNA and aminotransferases (ALT) ('HBeAg-positive chronic hepatitis'). Spontaneous and treatment-related HBeAg seroconversion with subsequent remission of liver disease is most common in this phase. In patients with perinatally acquired infection, the first phase is usually characterized by the presence of HBeAg and high levels of serum HBV DNA but normal ALT (immune tolerant phase). During this phase, there is a very low rate of spontaneous HBeAg clearance and treatment is usually ineffective in inducing sero-

conversion. Transition from the replicative phase to an inactive phase (inactive carrier-state) is characterized by spontaneous HBeAg clearance, low or sometimes undetectable serum levels of HBV DNA and normal ALT levels. These patients do not need to be treated with anti-viral agents. Some patients ultimately lose hepatitis B surface antigen (HBsAg) and this final phase is referred to as 'resolution' of infection. Another form of chronic hepatitis B ('HBeAg-negative chronic hepatitis') is characterized by high levels of HBV DNA (>100,000 copies/ml), elevated ALT and presence of HBe antibody (anti-HBe). These patients may have residual populations of wild type HBV or HBV variants that prevent the production of HBeAg. This form of chronic hepatitis is marked by a fluctuating course and spontaneous remissions are rare. Thus, anti-viral treatment is indicated.

The natural course of chronic hepatitis B is punctuated by spontaneous flares of disease activity [3]. Recurrent episodes of necroinflammation and regeneration may increase the risk of fibrosis and cirrhosis as well as carcinogenesis. A recent study found that whereas the relative risk of HCC among men with HBsAg alone was 9.6 compared to those without HBsAg, the risk increased to 60.2 when they were positive for both HBsAg and HBeAg [4]. There is also data to suggest that survival among cirrhotic patients is lower among those who are HBeAg positive [5]. These observations highlight the central role of virus replication in the outcome of HBV infection and the need to induce sustained suppression of HBV replication as early in the course of the disease as possible.

## 3. HBV DNA monitoring

The availability of molecular diagnostic assays has improved our understanding of the clinical manifestations and natural history of HBV infection and facilitated the monitoring of response to treatment [2]. Hybridization and signal amplification assays have sensitivity limits of  $10^5$ – $10^6$  copies/ml while target amplification assays such as

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polymerase chain reaction (PCR) assays are capable of detecting as little as 10–100 copies/ml of HBV DNA.

The major role of monitoring serum HBV DNA level is to assess disease activity and candidacy for anti-viral therapy and to determine response to treatment. The National Institutes of Health (NIH) workshop on management of Hepatitis B recommended that anti-viral treatment be considered in patients with HBeAg positive or HBeAg negative chronic hepatitis and HBV DNA  $>10^5$  copies/ml [2]. This value was arbitrarily chosen to include patients with detectable HBV DNA by non-amplified assays. The HBV DNA level associated with progressive liver disease has not been determined. HBV DNA level  $<10^5$  copies/ml was also recommended as the criteria for virological response. HBV DNA level can also be used to predict treatment response, although the correlation between pre-treatment serum HBV DNA level and response to nucleos(t)ide analogs is not as strong as response to interferon therapy.

#### 4. HBV genotypes

HBV is now classified into seven major genotypes (A–G) based on an inter-group divergence in the complete nucleotide sequence [2,6,7]. The geographical distribution of HBV genotypes is varied with genotype A being more common in Northwest Europe and North America, genotypes B and C being more common in Asia, and genotype D most common in Southern Europe and India. The distribution of genotypes E, F, G and the most recently reported genotype H is less clear. The most common pre-core mutation ( $G_{1896}A$ ) that blocks production of HBeAg is predominantly found in association with HBV genotypes B, C and D. Thus, HBeAg negative chronic hepatitis B is more common in Asia and Southern Europe.

Several studies suggest that HBV genotypes may influence HBeAg seroconversion, disease progression and even response to anti-viral therapy (Table 1). Patients with genotype C infection have been found to have a lower rate of spontaneous HBeAg seroconversion and higher rates of cirrhosis compared to those with genotype B [7–9]. Among interferon (IFN) treated patients, genotypes A and B have been reported to be associated with higher rates of anti-viral response than genotypes D and C, respectively [10,11]. These data suggest that future clinical trials of anti-viral therapy should be stratified for HBV genotype. The correlation between HBV genotype and response to other anti-viral therapies such as lamivudine and adefovir dipivoxil is unclear at this time. A recent report suggested that patients with HBV subtype ayw have a lower rate of lamivudine resistance compared to those with subtype adw [12].

#### 5. HBV variants

HBV replicates via reverse transcription of the pre-genomic RNA, and is therefore more prone to mutations than

other DNA viruses. Mutations have been described in all regions of the HBV genome. Mutations involving the pre-core and core promoter region have been most extensively studied [2,13–15]. The most common mutations include the G to A substitution at nucleotide 1896 ( $G_{1896}A$ ) resulting in a premature stop codon in the pre-core region and disruption of HBeAg production, and a dual mutation ( $A_{1762}T, G_{1764}A$ ) in the core promoter region that down regulates HBeAg production. These mutations usually emerge prior to or at the time of HBeAg seroconversion. Among patients who are anti-HBe positive, those with the  $G_{1896}A$  variant have been reported to have lower rates of sustained response to IFN treatment compared to those with wild type HBV [11]. In contrast, patients with HBeAg positive chronic hepatitis who have  $G_{1896}A$  variant appear to have higher rates of response to IFN therapy [16]. One explanation might be that these patients are on the way to spontaneous HBeAg seroconversion and IFN merely hastened the process. The relation between core promoter mutations and response to IFN therapy is less clear. In one study, sustained response to IFN was associated with a high number of mutations in the basic core promoter region among the HBeAg positive patients but the reverse was true for HBeAg negative patients [17]. The relation between pre-core and core promoter mutations and response to lamivudine and other anti-viral agents has not been studied.

#### 6. Management of patients with chronic HBV infection

Management of patients with hepatitis B should include thorough evaluation of HBV replication and liver disease, proper counseling on precautions to prevent transmission, detailed discussion regarding natural course of HBV infection and prognosis, and careful balance of treatment options.

The initial evaluation of patients with chronic HBV infection should include a thorough history and physical examination, with special emphasis on risk factors for coinfection, alcohol use, and family history of HBV infection and HCC. Laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for coinfection with hepatitis C and D virus, and human immu-

**Table 1**  
Clinical significance of HBV genotypes

|  |
|--|
| Geographical distribution                                      |
| A – Northwest Europe and North America                         |
| B – SE Asia  |
| C – Far East   |
| D – Mediterranean basin, India, Middle East                    |
| Spontaneous HBeAg seroconversion                               |
| B earlier than C   |
| Activity of liver disease and risk of progression to cirrhosis |
| C>B  |
| Response to IFN  |
| A better than D  |
| B better than C  |

**Table 2**  
**Definition of response to anti-viral therapy of chronic hepatitis B**

|                      |  |
|----------------------|--|
| Category of response |  |
| Biochemical (BR)     | Decrease of serum ALT to within the normal range   |
| Virological (VR)     | Decrease of serum HBV DNA to undetectable levels in non-amplified assays ( $<10^5$ copies/ml), and loss of HBeAg in patients who were initially HBeAg positive |
| Histological (HR)    | Decrease in histology activity index by at least two points compared to pre-treatment liver biopsy   |
| Complete (CR)        | Fulfill criteria of biochemical and virological response and loss of HBsAg   |
| Timing of response   |  |
| On-treatment         | Response during treatment  |
| Sustained            | Response that is maintained up to 6–12 months after cessation of treatment   |

nodeficiency virus (HIV) in those at risk. Because of the fluctuating course of HBV infection, serial testing for ALT, HBV DNA and HBeAg/anti-HBe over a 6–12 month period is often necessary to categorize the HBV replication level and activity of liver disease. In addition, a liver biopsy is recommended as part of the initial evaluation of patients with intermittent or persistent elevation of ALT levels. HCC surveillance should be considered in high-risk carriers, men over 45 years, persons with cirrhosis, and those with a family history of HCC.

Patients with chronic HBV infection should be counseled regarding lifestyle modifications and prevention of transmission. Heavy use of alcohol should be discouraged in all patients and abstinence recommended in those with cirrhosis. Counseling should include precautions to prevent transmission of HBV infection, and vaccination of sexual and household contacts.

## 7. Treatment

The main goal of treatment of chronic hepatitis B is to suppress HBV replication and to induce remission of liver disease before cirrhosis and HCC develop. Until now, interferon alfa (IFN) and lamivudine were the only two approved treatments for chronic hepatitis B. Recently, adefovir dipivoxil has been approved for use in patients with chronic hepatitis B in the US and Europe. Many new anti-viral and immunomodulatory therapies are being evaluated and may play a key role in the treatment of chronic HBV infection.

Response to therapy is usually defined as undetectable

HBV DNA in serum (using non-amplified assays), sustained loss of HBeAg with or without detection of anti-HBe (HBeAg seroconversion), and improvement in liver disease (normalization of ALT levels and decrease in necroinflammation or prevention of fibrosis progression in liver biopsies). At the recent NIH workshop on Management of Hepatitis B, it was proposed that definition and criteria of response to anti-viral therapy of chronic hepatitis B be standardized [2]. Response should be defined as biochemical (BR), virological (VR) or histological (HR), during treatment (at the end of treatment or maintained response during long-term therapy) or sustained 6–12 months off-therapy (Table 2).

## 8. Current status of approved treatments: safety and efficacy interferons (IFN)

IFN in general have more marked immunomodulatory and less potent anti-viral effects.

### 8.1. Efficacy in various categories of patients

#### 8.1.1. HBeAg positive chronic hepatitis

The effects of IFN in inducing virological and biochemical response has been well established. Meta-analyses have shown that a positive response can be achieved in 25–40% of HBeAg positive patients with elevated ALT within 12 months of initiating treatment [2,18,19]. In comparison, spontaneous loss of HBeAg was found in 10–15% of untreated controls, so a treatment-related benefit is only seen in approximately 15–25% of patients. The majority of responders have durable response with reactivation noted in only 10–20%, mostly within the first year of stopping therapy. Most patients who clear HBeAg continue to have low levels of HBV replication as determined by PCR assay. Long-term follow-up of some studies have shown that the 5-year cumulative rates of HBeAg clearance are similar or even higher in untreated patients so the main role of IFN may be to hasten viral clearance thereby reducing the duration of active liver disease [20,21]. IFN has been shown to have similar response in children with HBeAg clearance rates of about 30% among IFN treated patients compared to 10% of controls [2,20,22].

Loss of HBsAg with IFN treatment occurs in 5–10% of patients within 1 year of the initiation of treatment, increasing with time among sustained responders with 5-year cumulative rates of 11–20% in European studies [20,23] and up to 71% at 11 years in one US study [24]. However, delayed HBsAg loss has not been observed in Asian studies [25,26].

Few trials had been designed to assess IFN's effect on histological improvement. Studies assessing long-term outcome of IFN treatment are mostly retrospective and had many pitfalls including use of historical controls, small sample size, heterogeneity of treatment regimen, and limited event occurrence. These studies found that

IFN treated patients, especially the responders, tend to have lower rates of hepatic decompensation and liver-related deaths when compared to controls but the effect of IFN on HCC development is less clear [21,23,24].

Some HBeAg positive patients have normal or minimally elevated ALT despite high levels of HBV DNA ( $>10^5$  copies/ml). These patients have poor response to IFN ( $<10\%$  HBeAg loss) possibly related to immune tolerance [18].

#### 8.1.2. HBeAg negative chronic hepatitis

Response in this setting cannot be assessed by HBeAg loss, and is usually defined as undetectable serum HBV DNA by hybridization assays along with normalization of ALT level. A recent analysis showed that end-of-treatment virological response ranged from 38 to 90% in treated patients compared to 0–37% of controls [2]. The 12-month sustained response rates varied from 10 to 47% (average 24%) among the treated patients and 0% in the controls. Response is more durable in patients who received treatment for 12 months or longer. Among sustained responders, HBsAg clearance has been noted in up to 15–30% during long-term follow-up [2,27,28]. In addition, a recent study of 164 (103 treated) consecutive patients with HBeAg negative chronic hepatitis showed that IFN slowed histologic disease progression, and sustained responders had lower rates of death and HCC [28].

#### 8.1.3. Non-responders to IFN treatment

Most studies have shown that re-treatment with IFN of HBeAg positive patients who failed previous course of IFN is associated with low rates of subsequent response (average 15%) [29,30]. There are very little data on re-treatment of patients with HBeAg negative chronic hepatitis. A recent study reported a sustained response of 31% after a second course of IFN among 51 HBeAg negative patients who relapsed or had no response during previous IFN treatment [31].

#### 8.1.4. HBV DNA positive clinical cirrhosis

Patients with compensated cirrhosis appear to tolerate IFN and respond as well as patients with pre-cirrhotic chronic hepatitis B. However, patients with clinically evident cirrhosis have a high risk of serious infections and potentially fatal exacerbations of hepatitis even with low doses of IFN [32,33].

### 8.2. Factors predicting response to IFN

Among HBeAg positive patients, high pre-treatment ALT and low HBV DNA levels are the best predictors of response to IFN but these factors are also associated with a higher rate of spontaneous HBeAg seroconversion [2,18,21,27,34]. Recently, HBV genotype also has been suggested to play a role in IFN response [7,10,11]. Among patients with HBeAg negative chronic hepatitis,

no single pre-treatment factor is predictive of response to IFN while early biochemical response appears to be related to a higher rate of sustained response [2,27].

### 8.3. Role of prednisone priming

Steroid withdrawal is associated with a flare in serum ALT levels (reflecting a heightened immune response) and is sometimes followed by HBeAg seroconversion. Although pilot studies showed that sequential treatment with prednisone followed by IFN is more effective than IFN alone, this effect has not been uniformly observed in subsequent large-scale studies. A meta-analysis of seven studies showed that the rates of HBsAg, HBeAg and serum HBV DNA clearance were similar in patients who received prednisone followed by IFN vs. IFN alone [35]. A recent larger analysis showed that prednisone priming followed by IFN is followed by higher rates of HBeAg seroconversion suggesting that a subset of patients may benefit from this approach [36]. However, steroid priming increases the risk of severe flares and is not recommended as primary treatment, especially in patients with underlying cirrhosis.

### 8.4. Role of pegylated interferon in chronic hepatitis B

The addition of polyethylene glycol (PEG) molecule to IFN produces a product with significantly longer half-life and more sustained interferon activity. Two forms of pegylated IFN have been tested in patients with chronic hepatitis C and shown to have similar tolerability and higher rates of sustained virologic response compared to standard IFN. In a recent report of pegylated IFN alpha 2a in 194 patients with chronic hepatitis B, treatment with pegylated IFN alpha 2a (90, 180, or 270 mcg per week) for 24 weeks resulted in more rapid and greater decline in HBV DNA compared to standard IFN (4.5 MU thrice weekly) [37]. HBeAg seroconversion was observed in 37, 33, and 27% vs. 25% in the pegylated IFN groups vs. standard IFN, respectively. Phase III clinical trials are underway to assess the efficacy of pegylated IFN compared to lamivudine and combination of pegylated IFN + lamivudine in patients with both HBeAg positive and HBeAg negative chronic hepatitis B.

### 8.5. Dose regimen

The recommended dose for adults is 5 MU daily or 10 MU thrice weekly and for children 6 MU/m<sup>2</sup> thrice weekly with a maximum of 10 MU [34,38]. The recommended duration of treatment for patients with HBeAg positive chronic hepatitis B is 16–24 weeks. Data in support of a longer duration are scanty. One study reported that among patients who have not cleared HBeAg after 16 weeks of IFN, those randomized to continue treatment until week 32 had significantly higher rates of HBeAg clearance compared to those who stopped treatment [39]. Current data suggest that patients with HBeAg negative chronic hepatitis should be treated for at least 12 months but it is

unclear if extending treatment beyond 12 months will increase sustained response [2].

### 8.6. Adverse events

Treatment with IFN is associated with a wide spectrum of side effects including an influenza-like illness, fatigue, anorexia, weight loss, hair loss, bone marrow suppression, hypo- and rarely, hyper-thyroidism. The most troublesome side effect of IFN is emotional lability with anxiety, irritability, depression and rarely suicidal tendency.

## 9. Lamivudine (Epivir™-HBV, 3TC)

Lamivudine is the (–) enantiomer of 2',3'-dideoxy-3'-thiacytidine, which is phosphorylated to the triphosphate (3TC-TP) and competes with dCTP for incorporation into growing DNA chains causing chain termination.

### 9.1. Efficacy in various categories of patients

#### 9.1.1. HBeAg positive chronic hepatitis B

Three large randomized clinical trials involving 731 patients from the US, Europe and Asia have shown that lamivudine therapy for 1 year leads to HBeAg seroconversion in 16–18% of patients compared to 4–6% of untreated controls [40–44]. Histological improvement defined as reduction in necroinflammatory score >2 points occurred in 49–56% treated patients and in 23–25% controls. An extension of the treatment phase in the Asian study has shown that HBeAg seroconversion rates increase with the duration of lamivudine therapy from 17% at 1 year to 27, 40, 47 and 50% at 2, 3, 4 and 5 years, respectively [45]. This incremental increase in seroconversion rates was attributed to continued lamivudine treatment, however, untreated controls were not available for comparison. Results of the multi-center Asian trial and sub-set analysis of the US and international trials showed that oriental patients respond similarly to lamivudine as whites.

Experience with lamivudine in children is limited. A recent large, multi-center controlled trial involved 286 children, aged 2–17 years, with elevated ALT randomized to receive lamivudine (3 mg/kg/day up to 100 mg/day) or placebo for 52 weeks [46]. As in adults, a significantly higher proportion of treated children developed HBeAg loss compared to placebo controls (23 vs. 13%). The adverse event profile of the two groups was similar. Lamivudine resistant HBV mutants were detected in 18% of treated children.

HBeAg positive patients with normal ALT and high HBV DNA levels – as with IFN, lamivudine has very low efficacy in this group of patients [47,48]. HBeAg seroconversion rate was less than 10% at 1 year in patients with pre-treatment ALT <2 times normal and only 19% after 3 years of treatment.

#### 9.1.2. HBeAg negative chronic hepatitis B

Lamivudine has been shown to benefit patients with HBeAg negative chronic hepatitis B [49,50]. Virological and biochemical response has been seen in up to 70–96% of patients receiving 48 weeks of lamivudine therapy vs. <10% among patients on placebo. Rates of histological improvement have ranged from 20 to 95% [51]. However, the vast majority (~90%) of patients relapse once therapy is stopped [51,52]. This has led investigators to resort to indefinite duration of treatment. Unfortunately, sustained biochemical and virological response rates decrease over time due to development of drug resistance. In one study, complete response (biochemical and virological) was seen in 81% of patients initially but was maintained in only 69% during the second year, lamivudine resistant mutants increased from 19% at the end of year 1 to 44% at the end of 2 years [53]. Loss of HBsAg is unusual in these patients.

#### 9.1.3. Non-responders to IFN treatment

In a multi-center trial on IFN non-responders, 238 patients were randomized to receive lamivudine alone for 52 weeks, combination of lamivudine + IFN or no treatment. HBeAg seroconversion was seen in 18, 12 and 13% of patients, respectively [54]. These data suggest that patients who failed IFN treatment have similar virological response to lamivudine as treatment-naïve patients and re-treatment with combination of IFN and lamivudine did not confer any added benefit compared to lamivudine monotherapy.

#### 9.1.4. HBV DNA positive clinical cirrhosis

Lamivudine is a safer treatment than IFN in patients with decompensated cirrhosis in that it does not have any myelo-suppressive effect and seldom causes significant ALT flares during therapy [55]. Improvement in liver disease with decrease in Child–Turcotte–Pugh (CTP) score along with decreased need for liver transplantation has been observed in patients who completed a minimum of 6 months treatment [56]. Some patients, however, continue to have progression of their liver disease warranting a transplant while others die due to complications of cirrhosis during the first few months of treatment. A recent analysis of 154 patients confirmed that benefit of lamivudine was only evident in patients who managed to survive the first 6 months of treatment with estimated actuarial 3-year survival of 88%, but 16% of patients died during the first 6 months [57]. Thus, available data suggest that a subset of patients with less advanced liver disease may derive clinical benefit from lamivudine therapy but development of drug resistance may halt or reverse the initial clinical improvement. Moreover, virologic breakthrough may increase the risk of recurrent hepatitis B post-transplant. Careful patient selection along with optimal timing of treatment is needed to maximize the benefits of lamivudine in this group of patients.

### 9.1.5. Recurrent hepatitis B post-liver transplantation

Recurrent HBV infection post-transplant has been reduced to less than 10% by the use of combination prophylaxis of hepatitis B immune globulin (HBIG) and lamivudine [2,58]. A recent review of 166 patients transplanted for hepatitis B over a 17-year period at a single center showed that survival is significantly improved with 1 and 5-year patient survival rates of 86 and 72% [59]. Nevertheless, recurrent hepatitis B still occurs in a small percent of patients. Lamivudine has been used to treat patients with recurrent hepatitis B. In one multicenter study, 52 patients with recurrent hepatitis B were treated with open label lamivudine for 52 weeks [60]. HBV DNA became undetectable in 60%, and 31% of HBeAg positive patients lost HBeAg. Loss of HBsAg was seen in 6%. Virological response was accompanied by biochemical and histological improvement. However, lamivudine resistant mutations were detected in 27% of patients, in some this was accompanied by clinical deterioration. This and other smaller studies confirm the efficacy of lamivudine in treating recurrent hepatitis B post-transplant, but the long-term benefits are limited by the development of drug resistance.

### 9.2. Predictors of response to lamivudine

Among patients who are HBeAg positive, pre-treatment serum ALT is the strongest predictor of response [47,48]. A recent analysis of four Phase III trials (where a total of 406 patients received lamivudine for 1 year) showed that pre-treatment serum ALT and histologic activity index were the most important predictors of lamivudine-induced HBeAg loss [48]. HBeAg seroconversion occurred in 2, 9, 21 and 47% patients with pre-treatment ALT levels within normal, 1–2 times normal, 2–5 times normal and more than 5 times normal; while the corresponding figures for 196 patients in the placebo group were 0%, 5, 9 and 15%, respectively. Among children, HBeAg seroconversion rate is also higher in those with pre-treatment ALT >2 times normal (34 vs. 16%) [46]. There are no data on predictors of response to lamivudine in HBeAg negative patients.

### 9.3. Long-term outcome of lamivudine therapy

There are very limited data on the durability of HBeAg seroconversion after lamivudine is discontinued. Follow-up of patients from the Asian trial showed that 83% maintained HBeAg seroconversion after 6–36 (median 19) months. Although the mean duration of lamivudine treatment after HBeAg seroconversion was similar among patients who did and did not relapse, four of six patients who relapsed had a much shorter duration of treatment ( $\leq 10$  months) after HBeAg seroconversion [61]. The impact of treatment duration on durability of lamivudine induced HBeAg seroconversion was demonstrated in another study from Korea [62]. In this study of 67 patients, those who received lamivudine for at least 4 months after HBeAg seroconversion had much lower rate of relapse compared to those who received treat-

ment for less than 2 months after HBeAg seroconversion (32 vs. 74% at 2 years). These data strongly suggest that additional treatment of at least four to six months may be needed after HBeAg seroconversion to decrease relapse. HBV genotype might be another important factor determining durability of HBeAg seroconversion. In a recent study from Taiwan with 12–60 month follow-up after HBeAg seroconversion, genotype B was the only predictor of sustained response [63].

Data on the long-term benefits of lamivudine treatment are limited. Controlled studies have shown that 1-year treatment with lamivudine is associated with histologic improvement in more than 50% of patients [40–42]. However, durability of the histologic improvement is uncertain in patients who have not achieved HBeAg seroconversion. Recent data suggest that with longer duration of treatment, drug resistant mutations might reverse the initial histologic benefit. In the Asian trial, 62 patients were evaluated with liver histology at 0, 1 and 3 years. Whereas necroinflammatory scores continued to improve at 1 and 3 years among patients without resistance, histologic scores worsened at 3 years after an initial improvement at 1 year in those with resistant mutations [64]. These data raise concerns over the continued use of lamivudine after development of drug resistance and the long-term clinical impact of lamivudine resistant mutants.

### 9.4. Dose regimen

The recommended dose for adults with normal renal function (creatinine clearance >50 ml/min) and no HIV infection is 100 mg daily given orally. Dose reduction is necessary for patients with renal insufficiency. Patients with HIV co-infection should be treated with 150 mg bid doses in addition to other anti-retroviral therapies. The recommended dose for children is 3 mg/kg up to 100 mg.

For patients with HBeAg positive hepatitis, lamivudine should be administered at least for 1 year to achieve a reasonable rate of HBeAg seroconversion. Based on currently available data, it might be prudent to maintain lamivudine for 4–6 months after achieving HBeAg seroconversion to decrease the chance of post-treatment relapse. Whether lamivudine should be discontinued in patients who have sustained HBeAg loss but no detectable anti-HBe remains to be determined. For patients who do not have HBeAg seroconversion at the end of 1 year, treatment may be continued if there is no evidence of breakthrough infection as rates of HBeAg seroconversion increase with longer duration of treatment. The decision to continue lamivudine must weigh the potential benefits against the risks of developing resistance. Patients who discontinue treatment should be closely monitored as acute exacerbations of hepatitis and hepatic decompensation may occur even in patients who have had HBeAg seroconversion [45,65–67]. Reinstitution of lamivudine treatment is usually effective in

controlling exacerbations in patients who have not developed breakthrough infection.

For patients with HBeAg negative chronic hepatitis B, relapse can occur even when treatment is stopped after serum HBV DNA has become undetectable by PCR assay. Because of the high rate (~90%) of relapse after 1 year of therapy, longer course of treatment is recommended but the optimal duration is unclear.

For patients with lamivudine resistance, the options include continue treatment in those with low HBV DNA and ALT levels, discontinue treatment and monitor for hepatitis flares, or add anti-viral agents such as adefovir, which are effective in suppressing lamivudine resistant HBV. Two recent reports from Asia suggest that discontinuation of lamivudine in patients with resistant mutants is not associated with increased frequency of hepatitis flares or decompensation compared to those who remained on treatment [68,69]. Thus, stopping lamivudine is a reasonable option in immunocompetent pre-cirrhotic patients but discontinuation of lamivudine should not be attempted in patients with underlying cirrhosis or immunosuppression unless they have been switched to 'salvage' therapy such as adefovir.

#### 9.5. Adverse effects

In general, lamivudine is very well tolerated. Various adverse events including a mild (two to three fold) increase in ALT level have been reported in patients receiving lamivudine, but these events occurred in the same frequency among the controls.

#### 9.6. Lamivudine resistance

Selection of lamivudine resistant mutants is the main concern with lamivudine treatment. Three mutations in the polymerase (P) gene have been clearly shown to confer resistance to lamivudine. They include methionine to valine or isoleucine (M204V/I) substitutions involving the YMDD locus in domain C and leucine to methionine substitution (L180M) in domain B [70]. Lamivudine resistance is usually manifested as 'breakthrough' infection defined as reappearance of HBV DNA in serum using non-amplified assay on two or more occasions after its initial disappearance. Breakthrough infection can also result from non-compliance. M204V/I mutations have been detected in 14–32% of HBeAg positive patients after 1 year of lamivudine treatment [40,43,44]. In the multi-center Asian study, the rates of lamivudine resistant mutations increased from 14% in year 1 to 38, 49, 66, and 69% after 2, 3, 4 and 5 years of treatment, respectively [71]. Retrospective analysis of an integrated database of four studies identified non-Asian ethnicity, high pre-treatment serum HBV DNA level, male sex, and high body mass index as factors that correlated with the development of lamivudine resistance [48]. Other factors that have been reported to be associated with lamivudine resistance include high pre-treatment ALT level,

serum HBV >10<sup>3</sup> copies/ml after 6 months of treatment, and HBV subtype [12]. Although virological response has been shown to be higher among patients with HBV genotype B compared to patients with genotype C (HBeAg seroconversion 23 vs. 11%), the rates of lamivudine resistance appear to be similar [72]. The rates of lamivudine resistance in HBeAg negative chronic hepatitis B appear to be more variable, 0–27% at 1 year and 10–56% at 2 years [73].

### 10. Adefovir dipivoxil (bis-POM PME A)

Adefovir dipivoxil is an orally bioavailable pro-drug of adefovir, a nucleotide analog of adenosine monophosphate [2,74,75]. It can inhibit both the reverse transcriptase and DNA polymerase activity and is incorporated into viral DNA causing chain termination. Adefovir at a dose of 10 mg daily has been recently approved for use in patients with chronic hepatitis B in the US and Europe.

Phase I/II clinical trials demonstrated that adefovir in doses ranging from 5 to 60 mg daily was effective in suppressing HBV replication. Two placebo-controlled phase III studies involving HBeAg positive and HBeAg negative patients with chronic hepatitis B have been completed.

#### 10.1. HBeAg positive chronic hepatitis B

In the phase III study, 515 patients were randomized to receive 10 or 30 mg of adefovir or placebo for 48 weeks. The rate of histologic response ( $\geq 2$  point decrease in Knodell necroinflammatory score with no worsening of fibrosis) was significantly greater with both doses of adefovir compared to placebo (53–59% vs. 25%) [76,77]. HBeAg loss was observed in 11, 24 and 27% and HBeAg seroconversion was seen in 6, 12 and 14%, respectively of patients receiving placebo, adefovir 10 mg and 30 mg, respectively.

#### 10.2. HBeAg negative chronic hepatitis B

In the phase III trial, 184 patients were randomized to receive 10 mg of adefovir vs. placebo for 48 weeks. The rate of histologic response was significantly higher among the treated patients, 64 vs. 33% controls [78]. Normalization of serum ALT and undetectable HBV DNA by PCR was achieved in 72 vs. 29% and 51 vs. 0%, respectively.

#### 10.3. Lamivudine resistant hepatitis B

Adefovir has been shown to be effective in suppressing not only wild type but also lamivudine resistant HBV mutants (single as well as double mutants) in clinical studies [75,79,80]. In one compassionate use study, 128 patients with decompensated cirrhosis were treated with 10 mg dose of adefovir. A 4 log reduction in HBV DNA levels was observed. HBV DNA suppression was sustained during the course of the study, and virologic response was accompanied by stable or decreased ALT level and CTP score

[81]. In this study 196 patients with recurrent hepatitis B post-liver transplantation were treated with adefovir at a dose of 10 mg. A 3–4 log reduction in HBV DNA was seen after 48 weeks of treatment [81]. Preliminary results of an ongoing randomized trial of adefovir monotherapy vs. adefovir + lamivudine combination therapy showed that reduction in HBV DNA levels after 48 weeks of therapy was similar in both treatment groups suggesting that adefovir alone is adequate in the suppression of lamivudine resistant HBV mutants [82]. These data are promising but longer follow-up is needed to establish the long-term efficacy of adefovir dipivoxil in patients with lamivudine resistant HBV mutants.

#### 10.4. Dose regimen

The recommended dose of adefovir is 10 mg daily. Dosing intervals should be adjusted in patients with renal insufficiency. The optimal duration of treatment is unknown but is likely to be more than 1 year. To date, there are no data on the durability of response after treatment discontinuation. The lack of reported resistance suggests that continued treatment will result in further viral suppression and sustained response may be achieved in an increasing proportion of patients during extended treatment. However, there are no data to support this hypothesis. Furthermore, the long-term safety of adefovir remains to be proven.

#### 10.5. Adverse events

To date, adefovir resistant mutations have not been observed [83]. The major concern with adefovir is nephrotoxicity, which was frequent with doses of 30 mg or higher [75,76].

Significant increase in serum creatinine ( $>0.5$  mg/dl) was not observed in the phase III trials of patients with compensated liver disease in which 10 mg dose was used, but in approximately 20% of pre- and post-liver transplant patients [75,81]. Although the latter patients have other factors that contributed to renal insufficiency, the long-term safety of adefovir remains to be established.

## 11. Other therapies

### 11.1. Famciclovir

Famciclovir is the oral pro-drug of penciclovir, an acyclic deoxyguanosine analog. Penciclovir triphosphate (PCV-TP) competes with dGTP for incorporation into the nascent HBV DNA chains and for the priming of reverse transcription. A phase III clinical trial of 417 patients with HBeAg positive chronic hepatitis B found a higher rate of HBeAg seroconversion in patients receiving famciclovir 500 mg thrice daily compared to placebo (9 vs. 3%) [84]. However, there was no significant difference between placebo and famciclovir 1500 mg given once daily. A significant histo-

logic improvement was also not evident among the famciclovir treated patients.

Drug resistant mutants have been reported with long-term famciclovir treatment. The most common mutation associated with famciclovir resistance is L180M while mutations in the YMDD locus have not been reported [85]. Given the low virological response rates, potential risk of drug resistance, and need for thrice daily administration, the role of famciclovir in the management of chronic hepatitis B is limited.

### 11.2. Emtricitabine/coviracil (FTC)

FTC is a cytosine nucleoside analog with potent anti-viral activity against HBV and HIV [2]. Because of the structural similarity with lamivudine (3TC), long-term treatment with emtricitabine may select the same resistant mutants. In one phase II study, 98 patients (77 HBeAg positive and 21 HBeAg negative) were randomized to receive 25, 100, 200 mg dose daily of emtricitabine [86]. At 48 weeks, loss of HBeAg was seen in 40% of 77 HBeAg positive patients (range 32–50%). Viral resistance (M204I/V  $\pm$  L180M) was seen in 12% in the 100 mg group and in only 6% in the 200 mg group. Among patients with HBeAg negative hepatitis, normalization of serum ALT was seen in 95% and HBV DNA became undetectable in 76%. Phase III clinical studies are ongoing.

### 11.3. Entecavir

Entecavir is an orally administered guanosine analog with potent anti-viral activity against HBV in in vitro studies and studies in woodchucks. In woodchucks with chronic woodchuck hepatitis (WHV), treatment with entecavir has resulted in decreased incidence of HCC with increased survival [87]. A phase II dose-finding study in humans showed that daily doses of 0.1 and 0.5 mg of entecavir led to greater reduction in HBV DNA compared to 100 mg dose of lamivudine [88].

Entecavir can inhibit replication of lamivudine resistant mutants in vitro but the effect on the mutants (especially the double mutants) is less compared to that on wild type HBV [89]. In one large double-blind study of 181 patients with lamivudine resistant HBV mutants (120 HBeAg positive and 60 HBeAg negative), patients were randomized to three doses of entecavir (0.1, 0.5 and 1.0 mg) daily vs. continuing 100 mg of lamivudine daily for 48 weeks [88]. Preliminary analysis at 24 weeks showed that HBV DNA was undetectable (bDNA assay) in 75 and 50% of patients treated with 1.0 and 0.5 mg of entecavir compared to about 15% each in the 0.1 mg entecavir and 100 mg lamivudine group. Entecavir was well tolerated with a safety profile similar to lamivudine. Phase III clinical studies are ongoing.

## 12. Other new anti-viral agents

### 12.1. L-Nucleosides

These are a class of simple ‘unnatural’ nucleosides (natural nucleosides with  $\beta$ -L-configuration) with potent inhibitory effect on HBV [2]. They include L-2'-deoxycytidine (L-dC), L-thymidine (L-dT), and L-2'-deoxyadenosine (L-dA). L-dC and L-dT have both been shown to be effective in suppressing HBV replication in humans [90,91]. In a phase IIA study, 30 patients with HBeAg positive hepatitis B were given escalating doses (25, 50, 100, 200, and 400 mg) of L-dT daily for 4 weeks [91]. Marked HBV DNA suppression (median decrease of 2.4–3.6 logs) was seen and all doses were well tolerated. It is unclear how effective these agents will be in suppressing lamivudine resistant mutants.

### 12.2. Clevudine (L-FMAU, 2'-Fluoro-5-methyl- $\beta$ -L-arabinofuranosyl)

Clevudine, a pyrimidine nucleoside analog, is a potent inhibitor of HBV replication in vitro. In woodchucks infected with WHV, clevudine administration resulted in as much as a 9-log reduction in HBV DNA [92]. In a phase I/II dose-escalation study, 25 chronic hepatitis B patients (HBeAg positive and negative) were given 10, 50 or 100 mg of clevudine once daily for 4 weeks [93]. All doses caused a median reduction of >2 log reduction in HBV DNA by end of 4 weeks and were well tolerated. HBV DNA suppression was sustained with median serum HBV-DNA levels remaining below pre-treatment level during the 24-week follow-up.

## 13. Combination therapies

Monotherapy with a single anti-viral agent or IFN has so far proven to be insufficient in eradicating HBV infection in the majority of patients. In patients with HIV and hepatitis C, combination therapies have been demonstrated to be more effective in suppressing or eliminating viral infection [2]. Potential advantages of combination therapy include additive or synergistic anti-viral effects along with decreased incidence of or delay in development of drug resistance. However, there may be increased cost, and increased risk of drug toxicity as well as drug-drug interactions.

### 13.1. IFN and lamivudine

#### 13.1.1. Treatment naïve patients

In one large multinational trial, 226 HBeAg positive patients were randomized to receive lamivudine monotherapy for 52 weeks, IFN alone for 16 weeks or lamivudine for 8 weeks followed by combination of lamivudine + IFN for 16 weeks [42]. HBeAg seroconversion rates at week 52 were 18, 19 and 29%, in the three groups, respectively (NS) based on intention-to-treat analysis but HBeAg sero-

conversion rate was significantly higher in the combination group compared to lamivudine monotherapy (36 vs. 19%,  $P < 0.05$ ) when per-protocol analysis was performed. Another study of 151 patients with HBeAg positive hepatitis B found that combination of IFN (9 MU tiw) + lamivudine (100 mg daily) for 24 weeks was associated with significantly higher rate of HBeAg seroconversion (33 vs. 15%) and histological improvement (46 vs. 27%) compared to lamivudine monotherapy for 52 weeks [94].

In one study of HBeAg negative chronic hepatitis B, 50 patients were given either lamivudine monotherapy or combination of IFN + lamivudine for 12 months. Sustained virological response was similar in both groups (17 vs. 19%), however, the combination appeared to prevent or delay the emergence of YMDD variants [95].

These data suggest that IFN + lamivudine combination may improve virological and histological response rates compared to monotherapy and may also decrease/delay drug resistant mutants in some patients but larger studies are needed to confirm these findings.

#### 13.1.2. IFN non-responders

One trial involved 238 IFN non-responders randomized to receive lamivudine for 52 weeks, lamivudine for 8 weeks followed by combination of lamivudine and IFN for additional 16 weeks, or placebo [54]. Lamivudine monotherapy was associated with a higher likelihood of HBeAg seroconversion (18 vs. 12 and 13%, respectively), and histologic improvement (52 vs. 32 and 25%, respectively) compared to the other two treatment groups. However, shorter duration of lamivudine therapy (24 vs. 52 weeks) in the combination group and variable timing of the second biopsy (28 weeks post-treatment in the combination group vs. on treatment in lamivudine only group) make it difficult to determine if combination therapy offered any additional benefit in these patients.

The combination of interferon + ribavirin has been studied in patients with chronic hepatitis B but the number of patients was small and it is unclear if addition of ribavirin contributed to the response [96].

### 13.2. Lamivudine and famciclovir

In vitro and in vivo studies in woodchucks have shown that lamivudine + penciclovir have additive or synergistic anti-viral effects. One pilot study found that a short course of combination therapy of lamivudine and famciclovir in HBeAg positive patients have added anti-viral efficacy [97]. It is unclear, however, if this combination will result in higher rates of sustained virological response or lower rates of drug resistant mutants.

## 14. Novel anti-viral approaches

Several innovative anti-viral approaches have been evaluated in vitro as well as in animal models of chronic hepa-

**Table 3**  
**Response to anti-viral therapy of HBeAg positive chronic hepatitis B**

|                                    | IFN        |         | Lamivudine |         | Adefovir |         |
|------------------------------------|------------|---------|------------|---------|----------|---------|
|                                    | 12–24 week | Control | 52 wk      | Control | 48 wk    | Control |
| Loss of serum HBV DNA <sup>a</sup> | 37         | 17      | 44         | 16      | 21       | 0       |
| Loss of HBeAg                      | 33         | 12      | 17–32      | 6–11    | 24       | 11      |
| HBeAg seroconversion               |            | Δ18     | 16–18      | 4–6     | 12       | 6       |
| Loss of HBsAg                      | 7.8        | 1.8     | < 1        | 0       | 0        | 0       |
| Normalization of ALT               |            | Δ23     | 41–72      | 7–24    | 48       | 16      |
| Histologic improvement             | NA         | NA      | 49–56      | 23–25   | 53       | 25      |

<sup>a</sup> IFN and lamivudine-hybridization assay, adefovir-PCR assay. Results expressed as %; Δ, difference in response; NA, not available.

titis [2]. They have not yet been proven effective in the management of patients with chronic hepatitis B infection. These include selective targeting of anti-viral agents to the liver, anti-sense molecules or ribozymes, and alfa-glucosidase inhibitor derivatives that inhibit proper folding and export of viral structural proteins.

Non-specific immunomodulatory therapy has proved to be unsuccessful in treating chronic HBV infection. The most promising candidate is thymosin, thymic-derived peptides that stimulate T cell function. It is well tolerated but data on efficacy are conflicting. Earlier small studies have found that thymosin was beneficial. In a study from Taiwan, virologic response was not significantly different at the end of treatment but patients who received thymosin had higher rates HBeAg clearance at month 18 (41 and 27% with thymosin given for 26 or 52 weeks, respectively compared to 9% with placebo) [98]. In a large double-blind randomized controlled trial in the US, only 14% of treated patients vs. 4% of controls cleared HBeAg [99]. A recent meta-analysis of five trials involving 353

patients showed that the odds ratio of virological response with thymosin over placebo at the end of treatment and at 6 and 12 months follow-up was 0.56, 1.67 and 2.67. This increased trend in response after cessation of treatment suggests that the therapeutic effect of thymosin is delayed [100].

### 15. HBV-specific immunomodulation

Several HBV-specific immunomodulatory therapies have been recently developed some of which have shown promise including S and pre-S antigen vaccines, DNA vaccination and T cell vaccines [2]. It remains to be determined if any of these modalities will be effective in viral clearance and disease remission in patients with chronic HBV infection. Adoptive immune transfer through bone marrow transplantation from donors who are anti-HBs and anti-HBc positive has been reported to result in clearance of

**Table 4**  
**Comparison of three approved treatment of chronic hepatitis B**

|  | IFN          | Lamivudine                     | Adefovir <sup>a</sup>     |
|--|--------------|--------------------------------|---------------------------|
| Indications                            |              |                                |                           |
| HBeAg + , normal ALT                   | –            | –                              | –                         |
| HBeAg + chronic hepatitis              | +            | +                              | +                         |
| HBeAg- chronic hepatitis               | +            | +                              | +                         |
| Decompensated cirrhosis                | –            | +                              | +                         |
| Duration of treatment                  |              |                                |                           |
| HBeAg + chronic hepatitis              | 4–6 months   | > 1 year                       | > 1 year                  |
| HBeAg- chronic hepatitis               | 1 year       | ≥ 1 year                       | ≥ 1 year                  |
| Decompensated cirrhosis                | NA           | Indefinite                     | Indefinite                |
| Durability of response                 |              |                                |                           |
| HBeAg + chronic hepatitis              | 80–90%       | 50–80%                         | Unknown                   |
| HBeAg – chronic hepatitis <sup>b</sup> | 20–25%       | ~ 10%                          | Unknown                   |
| Route                                  | Subcutaneous | Oral                           | Oral                      |
| Side effects                           | Many         | Negligible                     | Potential nephrotoxicity  |
| Contraindications                      | ++           | –                              | –                         |
| Drug resistance                        | –            | ~ 20%, year 1<br>~ 70%, year 5 | None, year 1              |
| Cost                                   | High         | Low <sup>c</sup>               | Intermediate <sup>c</sup> |

<sup>a</sup> Approved in the United States only.

<sup>b</sup> After 12 months of treatment.

<sup>c</sup> Based on treatment duration of 1 year.

**Table 5**  
**Recommendations for treatment of chronic hepatitis B**

| HBeAg | HBV DNA <sup>a</sup> | ALT       | Treatment strategy   |
|-------|----------------------|-----------|--|
| +     | +                    | Normal    | Low efficacy for both IFN, lamivudine and adefovir<br>Observe patient, consider treatment when ALT becomes elevated  |
| +     | +                    | Elevated  | IFN, lamivudine or adefovir<br>IFN non-responders and patients with contraindications to IFN, → lamivudine or adefovir<br>Patients with lamivudine resistance → adefovir   |
| –     | +                    | Elevated  | IFN, lamivudine or adefovir.<br>Long-term treatment required<br>IFN non-responders and patients with contraindications to IFN, → lamivudine or adefovir<br>Patients with lamivudine resistance → adefovir              |
| –     | –                    | Normal    | No treatment required  |
| ±     | +                    | Cirrhosis | Compensated: IFN (close monitoring required), lamivudine or adefovir<br>Decompensated: lamivudine or adefovir. Optimal timing of therapy unknown<br>Patients with lamivudine resistance → adefovir<br>Liver transplant |
| ±     | –                    | Cirrhosis | Compensated: observe<br>Decompensated: liver transplant  |

<sup>a</sup> HBV DNA >10<sup>5</sup> copies/ml, this value is arbitrarily chosen and may be lower for patients with HBeAg negative chronic hepatitis B and those with decompensated cirrhosis.

HBV in recipients with chronic HBV infection [101]. However, the risks of the procedure preclude its routine use as treatment of chronic hepatitis B.

## 16. Conclusions

Significant advances have been made in molecular diagnosis and treatment options of hepatitis B in the past decade. Management of patients with chronic hepatitis B should be tailored according to patients' age, co-morbid conditions, HBV replication and liver disease. It is anticipated that detailed characterization of virologic characteristics: HBV genotypes, molecular variants, and quantification of serum HBV DNA levels will be part of routine patient management, and combination therapies with higher rates of sustained virologic response and resultant improvement in clinical outcome will be available in the next decade.

At the moment, existing therapies of hepatitis B: IFN, lamivudine and most recently adefovir dipivoxil, have limited long-term efficacy (Tables 3 and 4). Thus, careful balance of patient's age, severity of liver disease, likelihood

of response and potential adverse events and complications is needed before treatment is recommended (Table 5).

HBV carriers to be considered for therapy should be those with chronic hepatitis B (HBeAg positive or negative) with elevated serum ALT and/or moderate to severe hepatitis on biopsy. Except for patients with decompensated cirrhosis, IFN, lamivudine or adefovir dipivoxil may all be used as initial therapy. The advantages of IFN include finite duration of treatment, lack of resistant mutants, and durable response. The disadvantages of IFN are costs, need for parenteral administration, and side effects. Lamivudine is more economical (if given for 1 year only) and is well tolerated. However, the durability of response is uncertain and the long-term clinical significance of the resistant mutants is concerning. Compared to lamivudine, adefovir dipivoxil has similar on-treatment response. The advantage of adefovir is the lack of drug resistance to date, but its long-term safety especially in patients who are susceptible to renal insufficiency remains to be established. Thus, for patients who choose an oral anti-viral agent as the first line therapy, the options are to start lamivudine and add or switch to adefovir when the patient develops resistance to lamivudine or to start with adefovir.

The key issue for the future is the evaluation of combination therapies: two or more anti-viral agents or an anti-viral agent plus IFN (standard or pegylated) and the design of tailored therapies based on virological, immunological and clinical characteristics of the individual patient.

## Declaration

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