Oral Antivirals for Chronic Hepatitis B

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Four oral antiviral agents have been approved by the United States Food and Drug Administration (FDA) for the treatment of chronic hepatitis B: lamivudine, adefovir, entecavir, and telbivudine [1,2]. Each medication has an excellent safety profile but also has potential limitations for long-term management of patients who have chronic hepatitis B. In addition, each of these drugs was developed independently and was tested and approved as monotherapy; therefore, resistance resulting from the emergence of mutant strains of hepatitis B virus (HBV) is an important consideration in the selection of medications in patients who have chronic hepatitis B. Unlike pegylated interferon-alfa therapy, all the oral nucleoside/nucleotide analogues have been shown to be effective across ethnic groups and HBV genotypes [3–11], and studies with these agents have demonstrated that effective suppression of HBV replication is associated with histologic and clinical improvement. This article reviews the oral HBV antiviral agents in the order of their approval as well as promising agents currently in phase III clinical trials for the treatment of chronic hepatitis B. The efficacy and safety data of the four currently FDA-approved agents in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B are summarized in Tables 1 and 2.

Lamivudine

Lamivudine, the first oral agent approved for the treatment of chronic hepatitis B, in 1998, is a minus enantiomer of 2'-3' dideoxy-3'-thiacytidine.
It initially was approved in 1995 for treatment of patients who had HIV. Randomized, controlled trials have shown that lamivudine is safe and effective in both HBeAg-positive and HBeAg-negative chronic hepatitis B, but the high frequency of lamivudine-resistant mutations has proven to be a major limitation of lamivudine monotherapy [12,13].

**Hepatitis B e antigen–positive chronic hepatitis B**

In the national and international registration clinical trials of lamivudine, HBeAg seroconversion rates of 16% to 18% were observed after 1 year of treatment with 100 mg of lamivudine daily in previously untreated patients who had chronic hepatitis B [3,4,14]. The rates of HBeAg seroconversion increased with continued therapy and increased to 50% after 5 years of
treatment [12,13,15,16]. In these pivotal studies, lamivudine was superior to placebo in achieving histologic improvement (defined as a reduction of at least two points in the histologic activity index necroinflammatory score), including retardation in the progression of fibrosis. When these early trials were undertaken, HBV DNA measurements relied on relatively insensitive hybridization assays with a detection threshold of $10^5$ to $10^6$ virions/mL.

In a randomized, controlled trial of lamivudine among children (daily dose of 3 mg/kg, to a maximum dose of 100 mg/d), the HBeAg seroconversion rate was 22%, compared with 13% in the placebo group [17]. Among prior nonresponders to interferon-alfa treated in a placebo-controlled multicenter trial, HBeAg seroconversion occurred in 18% of lamivudine-treated patients, 13% of placebo-treated patients, and in only 12% of subjects treated with a combination of interferon and lamivudine [18]. Thus, in these registration trials, the response to lamivudine monotherapy was similar in treatment-naive patients and interferon nonresponders, and combination interferon/lamivudine treatment provided no additional benefit over lamivudine monotherapy in interferon nonresponders.

Table 2
Comparison of oral agents in treatment-naive patients with HBeAg-negative chronic hepatitis B*

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>100 mg</td>
<td>10 mg</td>
<td>0.5 mg</td>
<td>600 mg</td>
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<tr>
<td>Duration of therapy</td>
<td>52 weeks</td>
<td>48 weeks</td>
<td>48 weeks</td>
<td>52 weeks</td>
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<td>Control arm in pivotal trials</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Lamivudine</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Reduction of serum HBV DNA from baseline, log_{10} copies/mL</td>
<td>$-4.4$ to $-4.7^a$</td>
<td>$-3.9$</td>
<td>$-5.0$</td>
<td>$-5.2$</td>
</tr>
<tr>
<td>% Achieving undetectable serum HBV DNA at 1 year of therapy</td>
<td>60–73$^b$</td>
<td>51</td>
<td>90</td>
<td>88</td>
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<tr>
<td>Loss of HBSAg (%)</td>
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<td>0</td>
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<td>0</td>
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<td>Normalization of ALT (%)</td>
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<td>Histologic improvement (%)</td>
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<td>70</td>
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<tr>
<td>Safety and tolerability</td>
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<td>Similar to placebo</td>
<td>Similar to lamivudine</td>
<td>Similar to lamivudine</td>
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<tr>
<td>Resistance (%)</td>
<td>15–25</td>
<td>0 (4 years, 29%)</td>
<td>&lt;1 (4 years, &lt;1%)</td>
<td>3.5 (2 years, 8.6%)</td>
</tr>
</tbody>
</table>

* One-year data.

$^a$ Lamivudine used hybridization assay with quantitation limit of $10^5$ copies/mL; all others used the sensitive PCR assay.

$^b$ Not reported in registration trials of lamivudine but reported in entecavir and telbivudine registration trials, in which lamivudine was the control comparator.
Hepatitis B e antigen–negative chronic hepatitis B

Several earlier studies demonstrated the benefit of lamivudine therapy in patients who had HBeAg-negative chronic hepatitis B [19,20]. More recent trials, in which lamivudine was used as the control comparator for newer antivirals and in which polymerase chain reaction (PCR) assays were used for quantification of HBV DNA (sensitivity thresholds of \( \sim 10^2 \) virions/mL), showed that, after 1 year of lamivudine therapy, serum HBV was suppressed to undetectable levels in 71% to 72% of patients who had HBeAg-negative chronic hepatitis B [8]. When lamivudine treatment was stopped, however, approximately 90% of patients relapsed [21], and the percentage of patients maintaining undetectable serum HBV DNA levels decreased with increasing duration of lamivudine therapy as lamivudine resistance emerged over time [2,11].

Patients who have advanced fibrosis and compensated or decompensated cirrhosis

In a double-blind, randomized, controlled trial, Liaw and colleagues [22] from Taiwan measured indicators of hepatic decompensation in patients who had advanced hepatic fibrosis or cirrhosis and who were assigned randomly to receive lamivudine or placebo. The study was terminated prematurely after an interim analysis revealed significantly higher rates of both overall disease progression (7.8% versus 17.7%; \( P = .001 \)) and development of hepatocellular carcinoma (3.9% versus 7.4%; \( P = .047 \)) in the placebo group than in the lamivudine group. This landmark study is the basis for the recommendation that patients who have chronic hepatitis B, compensated cirrhosis, and detectable HBV DNA replication should be treated with antiviral agent(s).

Furthermore, several studies have demonstrated the safety and benefit of lamivudine therapy in patients who have decompensated cirrhosis [23–26]. Although the clinical improvement might take 3 to 6 months after the initiation of antiviral therapy, antiviral therapy in patients who have decompensated cirrhotic can result in a reversal of decompensation, prolonging survival and delaying or even rendering imminent liver transplantation unnecessary.

Durability of response

Posttreatment durability of HBeAg seroconversion in HBeAg-positive patients treated with lamivudine has ranged from 50% to 77% in published reports [27–29]. Factors associated with increased durability of lamivudine-induced HBeAg seroconversion include longer duration of consolidation treatment (defined as duration of continuous treatment beyond the time after HBeAg seroconversion), younger age, and lower HBV DNA level at the time of discontinuation of lamivudine [2,30]. In contrast, the durability of
lamivudine-induced viral suppression after 1 year of treatment in HBeAg-negative patients has been less than 10% [2].

**Lamivudine resistance**

Lamivudine resistance is discussed in depth in the article by Zoulim elsewhere in this issue. Briefly, lamivudine resistance emerged in 15% to 25% of patients treated for 1 year, increasing progressively during long-term treatment to about 40% at 2 years and to 70% at 5 years. Although clinical benefit may be maintained for a short time after the emergence of resistance, presumably because some lamivudine-associated mutants may be less fit, compensatory mutations eventually arise, allowing high-level HBV replication and HBV-associated liver injury to dominate the clinical picture and leading to a degradation in antiviral effect and clinical benefit.

**Dose regimen**

The recommended oral dose of lamivudine in adult patients who have creatinine clearance of greater than 50 mL/min is 100 mg once a day. The dose needs to be adjusted downwards for patients who have diminished renal function.

**Predictors of response**

In HBeAg-positive patients, the strongest predictor of an HBeAg response is pretreatment alanine aminotransferase (ALT) level. After 1 year of lamivudine treatment, recorded frequencies of HBeAg seroconversion were 2% in patients who had normal ALT levels, 9% in patients who had ALT levels between one and two times the upper limit of normal (ULN), 21% in patients who had ALT levels between two and five times the ULN, and 47% in those with ALT values exceeding five times the ULN [31].

**Safety**

Lamivudine is well tolerated, and its side-effect profile is indistinguishable from that of placebo. Almost 10 years of experience following its approval for routine use in chronic hepatitis B confirms lamivudine’s excellent safety profile.

**Adefovir dipivoxil**

Adefovir dipivoxil, a prodrug of adefovir, a nucleotide analogue of adenosine monophosphate, was approved for treatment of chronic hepatitis B in 2002.
**Hepatitis B e antigen–positive chronic hepatitis B**

The pivotal registration, phase III trial of adefovir compared with placebo demonstrated that a 48-week course of adefovir at a daily dose of 10 mg resulted in histologic improvement (53% versus 25%; \( P < .001 \)), increased HBeAg seroconversion (12% versus 6%; \( P = .049 \)), a more profound reduction in HBV DNA levels (median 3.5 log\textsubscript{10} copies/mL versus 0.6 log\textsubscript{10} copies/mL), and increased normalization of ALT values (48% versus 16%; \( P < .001 \)) [32]. As measured by a PCR assay (Roche Amplicor Monitor, Roche Molecular Systems, Inc., Branchburg, NJ) with a lower limit of detection of 400 copies/mL, HBV DNA levels were undetectable in 21% of adefovir-treated patients but in none of the placebo group (Table 1). Trial subjects who continued adefovir treatment beyond 1 year experienced additional reduction in HBV DNA and an increase in HBeAg seroconversion. Unfortunately, a misallocation error in randomization during the second year of the trial interfered with the integrity of the data, but in a selected subset of subjects in whom allocation was correct, a Kaplan-Meier projection suggested that, after a total of 144 weeks of adefovir treatment, 53% of patients achieved HBeAg loss, 46% achieved HBeAg seroconversion, serum HBV DNA was undetectable (by PCR) in 48%, and ALT had normalized in 80% [32]. Given the disappointingly low HBeAg seroconversion rate of only 12% at year 1 of adefovir, however, these 3-year projections are recognized to be overestimates. Moreover, up to 20% to 50% of patients receiving the 10-mg dose of adefovir seem to have a primary nonresponse, defined as a reduction in serum HBV DNA of less than 2 log\textsubscript{10} IU/mL after at least 24 weeks of therapy [2,33], and suppression of HBV DNA occurs more slowly and less reliably with adefovir therapy than with other oral agents.

**Hepatitis B e antigen–negative chronic hepatitis B**

The randomized, controlled, registration, phase-III trial in HBeAg-negative chronic hepatitis B involved 184 patients randomly assigned in a 2:1 ratio to receive adefovir or placebo for 1 year [5]. A 48-week course of adefovir at a daily dose of 10 mg, compared with placebo, resulted in histologic improvement (64% versus 33%; \( P < .001 \)), a more profound reduction in HBV DNA (median reduction of 3.91 log\textsubscript{10} copies/mL versus 1.35 log\textsubscript{10} copies/mL), and increased ALT normalization (72% versus 29%; \( P < .001 \)). As measured by a PCR assay (Roche Amplicor Monitor) with a lower limit of detection of 400 copies/mL, HBV DNA was undetectable in 51% of the adefovir-treated patients compared with 0% in the placebo group (\( P < .001 \)) (Table 2). Follow-up studies beyond week 48 showed that 144 weeks of continuous adefovir treatment resulted in long-term virologic responses; 79% of adefovir-treated patients achieved undetectable serum HBV DNA levels (with a lower quantitation limit of < 1000 copies/mL), and 69% achieved ALT normalization [34]. Furthermore, additional long-term
monitoring after 4 years of treatment in 55 patients and after 5 years of treatment in 70 patients showed continued histologic improvement and maintenance of undetectable serum HBV DNA levels in 65% of the 4-year and 67% 5-year patient cohorts [35].

**Lamivudine-resistant chronic hepatitis B**

An early pilot study of adefovir in patients who had lamivudine-resistant chronic hepatitis B showed no difference in virologic and biochemical responses between patients treated with adefovir alone (ie, who switched from lamivudine to adefovir) and those treated with the combination of adefovir and lamivudine (ie, adefovir added to lamivudine) for 1 year [36]. Furthermore, adefovir was effective in improving the hepatic function of patients who had decompensated HBV cirrhosis who had developed lamivudine resistance [37]. Patients who discontinued lamivudine and switched to adefovir monotherapy, however, were more likely to experience ALT flares than those randomly assigned to the combination regimen. In addition, more recent studies have shown that, in patients who have lamivudine-resistant chronic hepatitis B, adding adefovir to lamivudine prevents adefovir-resistant HBV, but switching to adefovir permits its emergence [38,39]. Therefore, adding adefovir to lamivudine is preferable to switching from lamivudine to adefovir for lamivudine-resistant chronic hepatitis B.

**Durability of response**

HBeAg seroconversion in HBeAg-positive patients was maintained in 69 of 76 (91%) patients at a median of 55 weeks after cessation of adefovir treatment [40]. These patients had received adefovir for a median of 41 weeks after HBeAg seroconversion had been documented. The longer patients were treated after seroconversion, the more likely they were to maintain HBeAg seroconversion.

**Adefovir resistance**

Although the rate of adefovir resistance is significantly lower than that of lamivudine resistance, novel “signature” mutations, including N236T (arginine-to-threonine substitutions) and A181V/T (alanine-to-valine or -threonine substitutions) [41,42], have been identified among adefovir-treated patients. Whether the A181T mutation is associated with actual virologic breakthrough is not clear. A long-term study in HBeAg-negative patients showed the cumulative frequency of genotypic adefovir resistance (not rates of virologic breakthrough, which are lower) to be 0%, 3%, 11%, 18%, and 29% at 1, 2, 3, 4, and 5 years of therapy, respectively [35]. A more comprehensive review of adefovir resistance appears elsewhere in this issue in the article by Zoulim.
Dose regimen

The recommended oral daily dose of adefovir in adult patients who have creatinine clearance of greater than 50 mL/min is 10 mg. According to the manufacturer’s guidelines, the dosage and/or frequency of adefovir administration should be adjusted downward in patients who have impaired renal function.

Predictors of response

Similar with lamivudine, HBeAg-positive patients who have high pre-treatment ALT values are more likely to achieve HBeAg seroconversion with adefovir [1,2]. One-year lamivudine-associated HBeAg seroconversion rates approximate 50% in patients who have ALT levels more than five times the ULN [31], but adefovir-treated patients who have similar ALT elevations experience HBeAg seroconversion rates of only 21%.

Safety

The side-effect profile of adefovir was similar to that of placebo in the pivotal phase III trials, but nephrotoxicity (reflected by a creatinine elevation ≥ 0.5 g/mL) has been reported in 3% of patients who had compensated liver disease after 4 to 5 years of adefovir therapy [35]. Higher rates of nephrotoxicity have been observed in patients who have undergone liver transplantation (12%) and in patients who have decompensated cirrhosis (28%), but it is unclear whether nephrotoxicity in these patient groups is related directly to adefovir therapy or to the effects of other confounding factors such as concurrent use of known nephrotoxic medications and hepatorenal physiology [37].

Entecavir

Entecavir is a carbocyclic analogue of 2’-deoxyguanosine and is a potent inhibitor of HBV replication at three DNA replicative sites.

Hepatitis B e antigen–positive chronic hepatitis B

In a phase III pivotal trial in which 715 patients were assigned randomly (1:1) to receive either 0.5 mg of entecavir daily or 100 mg of lamivudine daily, at week 48 entecavir was superior to lamivudine in rates of histologic, virologic, and biochemical responses [8]. Histologic improvement occurred in 72% in the entecavir group, compared with 62% in the lamivudine group. Similarly, serum HBV DNA was undetectable (< 300 copies/mL) in 67% of patients taking entecavir compared with 36% of patients taking lamivudine. The rates of HBeAg seroconversion, however, were indistinguishable in the two groups: 21% in the entecavir group and 18% in the lamivudine group.
After an additional year of therapy, 81% of entecavir-treated patients but only 39% of lamivudine-treated patients had undetectable serum HBV DNA [43]. Through 144 weeks of entecavir therapy, cumulative confirmed virologic responses (undetectable serum HBV DNA levels, < 300 copies/mL) occurred in 87% of patients, and ALT levels normalized in 85% [44]. After 3 years of entecavir therapy, HBeAg loss occurred in 49% and HBeAg seroconversion occurred in 39% of the initial 354 patients [44].

Hepatitis B e antigen–negative chronic hepatitis B

Similar to the pivotal registration trial in HBeAg-positive subjects, the phase III trial in HBeAg-negative patients showed that at week 48 entecavir was superior to lamivudine in the rates of histologic, virologic, and biochemical responses [9]. Histologic improvement occurred in 70% of the entecavir group, compared with 61% of the lamivudine group. Similarly, serum HBV DNA was undetectable in 90% of patients taking entecavir compared with 72% of patients taking lamivudine. ALT was normalized in 78% of the entecavir group and in 71% of the lamivudine group.

Lamivudine-resistant chronic hepatitis B

A phase III trial in which HBeAg-positive patients refractory or resistant to lamivudine therapy were assigned randomly to a 1-mg daily dose of entecavir or to 100 mg of lamivudine for 48 weeks demonstrated the superiority of entecavir over continuing lamivudine in the rates of histologic, virologic, and biochemical responses [45]. In lamivudine-refractory patients, 1 mg of entecavir suppressed HBV DNA levels to less than 300 copies/mL in 21% of patients by week 48 and in 34% by week 96 [46]. The role of entecavir in lamivudine-experienced chronic hepatitis B, however, is limited by the emergence of entecavir resistance that is favored by pre-existing lamivudine-resistant HBV. The rate of entecavir resistance, less than 1% at 4 years in treatment-naive patients, was 6% in lamivudine-resistant patients at the end of 1 year of therapy and increased to ~40% at the end of year 4 [46–49].

Durability of response

In the registration entecavir trial, the durability of HBeAg seroconversion was approximately 70% among HBeAg-positive patients who had achieved HBeAg seroconversion and who stopped entecavir therapy at 48 weeks [8,43].

Entecavir resistance

In nucleoside-naive patients, resistance to entecavir seems to be rare, with cumulative resistance rates of less than 1% through 1, 2, and 3 years of treatment [47,48]. Among those treated with entecavir for 4 years, resistance to
Entecavir was still less than 1% [49]. Resistance to entecavir requires a prior selection of the characteristic YMDD mutation (M204V/I), a hallmark of lamivudine resistance [50]. Thus, not surprisingly, viral breakthrough was seen in 16% of previously lamivudine-refractory patients after 96 weeks of entecavir therapy, in 35% after 144 weeks, and in 43% through 4 years of treatment [49]. Therefore, most authorities do not recommend entecavir monotherapy in lamivudine-resistant patients, even though the FDA has approved a higher dose (1 mg) for this population. A detailed discussion of entecavir resistance is given in the article by Zoulim elsewhere in this issue.

**Dose regimen**

The recommended oral daily dose of entecavir in patients aged 16 years or older with creatinine clearance of 50 mL/min is 0.5 mg for patients naive to nucleoside therapy and 1 mg for lamivudine-resistant patients. As with the other oral antiviral agents for hepatitis B, the dosage should be adjusted downwards for patients who have impaired renal function; for such patients, the dose can be calibrated by relying on the oral entecavir solution, which contains 0.05 mg/mL.

**Predictors of response**

Similar to lamivudine, in patients treated with entecavir, the rate of HBeAg seroconversion was higher in patients who had higher pretreatment ALT levels. HBeAg seroconversion rates were and 12% for those with baseline ALT levels less than two times the ULN, 23% for patients with baseline ALT levels between two and five times the ULN, and 39% in those with baseline ALT levels five times the ULN [51].

**Safety**

No significant difference in safety profiles has been observed between patients treated with entecavir and lamivudine [8,9]. Concern about the occurrence of pulmonary tumors in mice treated with high-dose entecavir in preclinical toxicology studies has not been realized in humans (and the histiocytic cell type from which these murine tumors originate does not exist in the human lung).

**Telbivudine**

Telbivudine, a β-L-2’-deoxythymidine, has potent antiviral activity against HBV. The phase III GLOBE trial, in which telbivudine was compared with lamivudine, was the largest HBV antiviral therapy trial to date and showed the superiority of telbivudine over lamivudine in the profundity of HBV DNA suppression and in achieving undetectable HBV DNA levels (< 300 copies/mL) at both 1 and 2 years of therapy.
Hepatitis B e antigen–positive chronic hepatitis B

The 1-year data from the GLOBE trial, in which 921 of 1367 enrolled patients were HBeAg positive, showed that telbivudine is superior to lamivudine in the profundity of HBV DNA suppression (6.5 versus 5.5 log_{10} copies/mL; \( P < .05 \)) and in the significantly higher proportion of patients achieving undetectable serum HBV DNA (60\% versus 40\%; \( P < .05 \)) [10]. No significant difference in ALT normalization between the two groups was observed, however. Furthermore, there was no apparent difference between the two groups in the rates of HBeAg loss and HBeAg seroconversion after 1 year of treatment. The final, 2-year data from the GLOBE trial showed that telbivudine continued to be superior to lamivudine in HBV DNA reduction (5.7 versus 4.4 log_{10} copies/mL; \( P < .05 \)) and in the proportion of patients who had achieved undetectable serum HBV DNA (56\% versus 39\%; \( P < .05 \)). Again, at the end of year 2, no difference was observed between the two groups in the rate of HBeAg loss and HBeAg seroconversion [11].

Hepatitis B e antigen–negative chronic hepatitis B

The 1-year data from the GLOBE trial, in which 446 of 1367 enrolled patients were HBeAg negative, showed that telbivudine is superior to lamivudine in the profundity of HBV DNA suppression (5.2 versus 4.4 log_{10} copies/mL; \( P < .05 \)) and in the proportion of patients who had undetectable serum HBV DNA (88\% versus 71\%) [10]. As was the case for HBeAg-positive patients, however, in the HBeAg-negative cohort, no significant difference was observed in ALT normalization between the two groups. The final, 2-year data from the GLOBE trial showed that in HBeAg-negative patients telbivudine continued to be superior to lamivudine in HBV DNA reduction (5.7 versus 4.4 log_{10} copies/mL; \( P < .05 \)) and in the proportion of patients who had achieved undetectable serum HBV DNA (82\% versus 57\%; \( P < .0001 \)) [11].

Lamivudine-resistant chronic hepatitis B

Because lamivudine and telbivudine are both \( l \)-nucleosides that are cross resistant, telbivudine is not recommended in patients who have lamivudine resistance. In vitro studies demonstrate that the M204V variant (one of the two YMDD mutations associated with lamivudine) actually is susceptible to telbivudine, but M204I associated with L180M, a common secondary mutation in lamivudine-resistant patients, is not.

Durability of response

The posttreatment durability of HBeAg seroconversion after telbivudine therapy was 83\% at a median of 35.2 weeks (range, 4–59 weeks) off treatment [11].
Telbivudine resistance

Defining virologic breakthrough as a level of HBV DNA 1 log₁₀ above the nadir, Lai and colleagues [11] reported a frequency of the genotypic resistance mutations with virologic rebound of 6% and 3.5% in HBeAg-positive and HBeAg-negative patients, respectively, at 1 year. These numbers represent a marked improvement over the 1-year frequency of lamivudine resistance. At 2 years, however, virologic rebound with genotypic mutations occurred in 21.6% of HBeAg-positive and in 8.6% HBeAg-negative patients, frequencies that were not competitive with those observed after entecavir.

Dose regimen

The recommended oral daily dose of telbivudine for patients aged 16 years or older with creatinine clearance greater than 50 mL/min is 600 mg. As with the other oral antiviral agents for hepatitis B, the dose should be adjusted downwards for patients who have impaired renal function.

Predictors of response and resistance

The more profound the suppression of HBV DNA, the more likely patients were to achieve HBeAg seroconversion. For those achieving undetectable HBV DNA ( < 300 copies/mL) after 6 months of telbivudine therapy, HBeAg seroconversion occurred in 46% of HBeAg-positive patients at 1 year; 95% and 83% maintained HBV DNA count below 300 copies/mL at 1 and 2 years, respectively [10,11]. Conversely, the rates of virologic rebound with genotypic mutations for HBeAg-positive patients who had undetectable HBV DNA at 6 months were extremely low: 1.1% at 1 year and 4% at 2 years [11,52]. In HBeAg-negative patients, 88% of those achieving undetectable HBV DNA after 6 months of therapy maintained viral suppression at 2 years. Among those achieving undetectable HBV DNA within 6 months of telbivudine therapy, virologic breakthrough with genotypic mutations occurred in 4% of HBeAg-positive (n = 203) and in 2% of HBeAg-negative (n = 178) patients through 2 years of continuous treatment [11,52].

A treatment algorithm based on a determination of HBV DNA at month 6 has been proposed for patients treated with telbivudine. Among those with complete suppression of HBV DNA at month 6, the likelihood that resistance will emerge through month 12 is so low that continued monotherapy can be justified. In contrast, if HBV DNA cannot be suppressed to less than 10³ to 10⁴ virions/mL within 6 months, the risk of resistance is sufficiently high to justify adding a second agent. For entecavir, however, resistance has been very rare (<1%) during the first 12 to 24 months, and an algorithm based on a 6-month milestone is unnecessary. Therefore, the 6-month decision node for telbivudine is not sufficiently compelling to justify choosing this drug over other, more potent, less resistance-prone agents.
Safety

Telbivudine was well tolerated, and its side-effect profile was similar to that of lamivudine, except that after 2 years of treatment grade 3 or 4 creatine kinase elevations were more frequent among telbivudine than lamivudine recipients (12.9% versus 4.1%) [52]. Most creatine kinase elevations were asymptomatic, but cases of myopathy were reported among telbivudine recipients several weeks to months after starting therapy.

Future therapies

Tenofovir

Tenofovir disoproxil fumarate, a nucleotide analogue that has been shown to be more potent than adefovir in suppressing HBV DNA, was approved by the FDA in 2001 for treatment of patients who have HIV infection. Studies in patients coinfected with HIV and HBV have shown consistently that tenofovir suppresses HBV DNA more profoundly than adefovir [53–55]. Limited resistance to tenofovir has been reported, but its clinical significance is unknown currently. In a retrospective study of 69 patients who had lamivudine-resistant HBV infection and varying comorbidities, including 24 who had for 6 to 59 months (mean, 33 months), at the end of the follow-up period 68 of the 69 patients had achieved undetectable HBV DNA levels without the emergence of resistance to tenofovir. A double-blind, randomized trial of adefovir versus tenofovir is in progress; in a preliminary report made in a press release, the manufacturer reported that at week 48, 71% in the tenofovir group (250 subjects) versus 49% in the adefovir group (125 subjects) experienced “complete” responses consisting of both a reduction of HBV DNA to less than 400 copies/mL and a two-point reduction in the necroinflammatory component of the histologic activity index ($P < .001$) [56].

Clevudine

Clevudine (L-FMAU) is a nucleoside analogue of the unnatural β-L configuration that has potent activity against HBV. A unique characteristic of clevudine is prolonged, sustained suppression of viral replication after withdrawal of treatment [57]. In a recent randomized clinical trial of 243 patients who had HBeAg-positive chronic hepatitis B, 182 patients were given a 30-mg daily dose of clevudine for 24 weeks followed by a further 24-week observation period without therapy. The median serum HBV DNA reduction at week 24 was 5.10$\log_{10}$ copies/mL [58]. Viral suppression in these patients was sustained with a 3.73 and 2.02$\log_{10}$ reduction at weeks 34 and 48, respectively, after cessation of therapy. Fifty-nine percent of patients had HBV DNA levels of less than 300 copies/mL after 24 weeks of clevudine therapy, and no resistance to clevudine was detected within the 24-week
period. In a similar clevudine study among patients who had HBeAg-negative chronic hepatitis B, 92% achieved undetectable HBV DNA after week 24 of treatment [59]. Currently, a phase III trial is in progress in which clevudine is being compared with adefovir (the approved drug that suppresses HBV DNA least profoundly) in both HBeAg-positive and HBeAg-negative chronic hepatitis B.

**Combination therapies**

To date, no randomized clinical trials have shown superior efficacy of a de novo combination regimen over monotherapy in achieving viral suppression. Therefore, combination therapy has not been recommended routinely for patients who have chronic hepatitis B. For patients who have lamivudine-resistant chronic hepatitis B, however, the addition of adefovir to lamivudine has been shown to preempt the emergence of adefovir resistance [38,39,60]. Furthermore, in certain categories of patients, particularly those who have decompensated cirrhosis associated with HBV infection, de novo combination therapy has been suggested [1], because the emergence of resistance has been shown to be associated with an increased risk of hepatic decompensation [22]. Several clinical trials to test the efficacy of combination therapy for chronic hepatitis B are already in progress or are being planned.

**Summary**

At present, a number of safe and effective oral medications are available for the treatment of patients who have chronic hepatitis B, and other promising agents are likely to become available in the near future. All these oral antiviral agents are well tolerated and are associated with few, if any, side effects. Moreover, histologic, virologic, serologic, and biochemical responses are at least as likely to occur during treatment with these oral agents as during a 12-month course of pegylated interferon therapy. Specifically, HBeAg serologic responses to the oral antivirals occur as frequently as such responses to pegylated interferon. Although the oral antivirals may require a longer treatment course, they are substantially better tolerated.

Lamivudine was the first oral agent approved. It has an outstanding safety profile and proven value in decompensated and compensated cirrhosis, but it is associated with too high a frequency of resistance for it to be recommended as first-line therapy for chronic hepatitis B. Entecavir and telbivudine are more potent than other agents in reducing serum HBV DNA levels. Entecavir is slightly more effective than telbivudine in reducing HBV DNA and has a trivial rate of resistance through several years of therapy. For telbivudine, resistance at year 2 is a major disadvantage. The original promise of adefovir, its relatively low frequency of early resistance, has
been tarnished by the emergence of substantial resistance during the third and fourth years of therapy and by its comparatively weak and gradual antiviral effect. Once current clinical trials of tenofovir are completed, adefovir is likely to be eclipsed entirely by tenofovir. Thus, for monotherapy of chronic hepatitis B, the two agents that seem most attractive are entecavir and tenofovir.

Effective use of oral antiviral agents in advanced HBV-associated liver disease, as demonstrated with lamivudine, is likely to be achievable also with the other oral agents that have supplanted lamivudine. Whether de novo combination therapy with oral agents should be a preferred, first-line option for treatment-naive patients awaits the outcome of clinical trials currently in progress.

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