Safety and efficacy of entecavir for the treatment of chronic hepatitis B

Melissa Osborn
Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA, USA

Abstract: Entecavir is a cyclopentyl deoxyguanosine analog that was approved for the treatment of the hepatitis B virus (HBV) in 2005. In Phase III trials, it showed potent HBV suppression with drops of 6- to 7-log copies/mL in HBV DNA at 1 year. In addition, rates of genotypic resistance in nucleos(t)ide-naïve patients are low, reaching only 1.2% after 6 years. Safety and efficacy have been established in compensated cirrhosis and HIV-coinfected patients. Studies in decompensated cirrhosis also show efficacy. Because of potent viral suppression and a large genetic barrier to resistance, entecavir is now a first-line choice in most HBV treatment guidelines and has become an integral part of the HBV treatment armamentarium.

Keywords: hepatitis B, therapy, entecavir

Introduction
During the past decade, four new drugs (adefovir, entecavir, telbivudine, and tenofovir) have been approved for the treatment of chronic hepatitis B virus (HBV), joining lamivudine as options for treatment. These new additions to the HBV arsenal have made decisions about treatment more complex. It has become increasingly important for treating physicians to understand the benefits and limitations of each agent as they decide on an initial or salvage regimen. This review will describe the efficacy of entecavir compared with other available drugs, as well as safety and resistance patterns. These issues are important to consider for drug sequencing in patients with chronic HBV.

Natural history of hepatitis B
Over 350 million people worldwide are chronically infected with HBV. The burden of disease is largely geographic, with South-East Asia and Sub-Saharan Africa being endemic. In these areas, transmission is primarily vertical or during childhood, where most infections go on to chronicity. In nonendemic areas, such as western Europe and the US, transmission is primarily sexual and occurs in early adulthood. When acquired later during life in this situation, 95% of acute HBV cases resolve spontaneously. Universal vaccination of infants in both endemic and nonendemic areas will no doubt change this epidemiology over the coming decades.

Once chronicity is established, the patient may undergo a period of immunotolerance, where HBV DNA levels are extremely high yet aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are normal. There is little to no inflammation present in the liver. In endemic areas, the immunotolerant period may last years, into the third decade of life. In nonendemic areas, however, the immunotolerant period...
Infection and Drug Resistance downloaded from https://www.dovepress.com/ by 54.70.40.11 on 08-Apr-2019
For personal use only.
Powered by TCPDF (www.tcpdf.org)

that has selective activity against the HBV polymerase. It is deoxythymidine. A similar to adefovir. Telbivudine is a l-nucleoside analog of log of adenosine monophosphate. Tenofovir is structurally similar to lamivudine, showing negligible effects on the priming reaction.

Clinical studies of efficacy

Phase I dose-ranging studies of entecavir demonstrated rapid and potent dose-related virologic suppression of HBV DNA.10,11 Because of shared resistance mutations between entecavir and lamivudine, clinical trials evaluated its use in both nucleos(t)ide-naïve patients and lamivudine-refractory patients. Efficacy was reduced in lamivudine-refractory patients harboring mutations in the tyrosine–methionine–aspartate–aspartate (YMDD) motif of the HBV polymerase; thus, a higher dosage of 1 mg daily was selected for development in these patients, compared with 0.5 mg/day for nucleos(t)ide-naïve patients.

Two multinational Phase III trials were conducted among nucleos(t)ide-naïve patients in HBeAg-positive patients12 and HBeAg-negative patients,13 both compared with lamivudine 100 mg daily. A Phase III trial was also carried out in China in a mixed population of both HBeAg-positive and HBeAg-negative patients. A smaller Phase III study compared entecavir with adefovir in patients with baseline HBV DNA levels >8 log copies/mL. Among HBeAg-positive patients, results at 48 weeks were similar across all studies with 68%–99% of patients achieving ALT normalization, and 58%–74% having an undetectable HBV DNA by sensitive polymerase chain reaction (PCR) assay (Table 1). The mean drop in HBV DNA over 48 weeks was 6–7 log copies/mL. On all of these parameters,
### Table 1 Summary of clinical trials of entecavir

<table>
<thead>
<tr>
<th></th>
<th>ALT normalization</th>
<th>Drop in HBV viral load (log copies/ml)</th>
<th>Undetectable HBV DNA by PCR</th>
<th>HBeAg loss</th>
<th>HBeAg seroconversion</th>
<th>HBsAg loss</th>
<th>HBsAg seroconversion</th>
<th>Histological improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside naïve, HBeAg positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al</td>
<td>68%</td>
<td>−6.9</td>
<td>67%</td>
<td>22%</td>
<td>21%</td>
<td>2%</td>
<td>72%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Leung et al</td>
<td>76%</td>
<td></td>
<td>58%</td>
<td>18%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yao et al</td>
<td>89%</td>
<td>−6.0</td>
<td>74%</td>
<td>18%</td>
<td>15%</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gish et al</td>
<td>87%</td>
<td></td>
<td>80%</td>
<td>31%</td>
<td>5%</td>
<td>2%</td>
<td>72%</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Nucleoside naïve, HBeAg negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lai et al</td>
<td>78%</td>
<td>−5.0</td>
<td>90%</td>
<td>19%</td>
<td>10%</td>
<td>8%</td>
<td>70%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yao et al</td>
<td>94%</td>
<td>−5.22</td>
<td>94%</td>
<td>19%</td>
<td>10%</td>
<td>8%</td>
<td>70%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shouval et al</td>
<td>27%</td>
<td></td>
<td>85%</td>
<td>0%</td>
<td></td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine refractory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al</td>
<td>68%</td>
<td>−5.06</td>
<td>26%</td>
<td>11%</td>
<td>4%</td>
<td>4%</td>
<td>55%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sherman et al</td>
<td>61%</td>
<td>−5.11</td>
<td>19%</td>
<td>10%</td>
<td>8%</td>
<td>8%</td>
<td>55%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yao et al</td>
<td>85%</td>
<td>−5.08</td>
<td>27%</td>
<td>6%</td>
<td></td>
<td>6%</td>
<td>60%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Suzuki et al</td>
<td>78%</td>
<td>−3.75</td>
<td>33%</td>
<td>15%</td>
<td></td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sherman et al</td>
<td>85%</td>
<td>−5.9</td>
<td>30%</td>
<td>16%</td>
<td>1.4%</td>
<td>0.7%</td>
<td>60%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yao et al</td>
<td>80%</td>
<td></td>
<td>47%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yao et al</td>
<td>65%</td>
<td></td>
<td>55%</td>
<td>17%</td>
<td>12%</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.
Table 2 Comparative efficacies at 1 year of available nucleos(t)ide analogs for the treatment of hepatitis B

<table>
<thead>
<tr>
<th></th>
<th>ALT normalization</th>
<th>Drop in HBV DNA (log copies/mL)</th>
<th>Undetectable HBV DNA by PCR</th>
<th>HBeAg loss</th>
<th>HBeAg seroconversion</th>
<th>HBsAg loss</th>
<th>HBsAg seroconversion</th>
<th>Histological response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>41%–72%</td>
<td>21%</td>
<td>32%</td>
<td>16%–17%</td>
<td>0%–2%</td>
<td>0%</td>
<td>14%–32%</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>48%–79%</td>
<td>−3.52</td>
<td>21%</td>
<td>13%–24%</td>
<td>8%–12%</td>
<td>2%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>68%–89%</td>
<td>−6.9</td>
<td>58%–74%</td>
<td>18%–22%</td>
<td>15%–21%</td>
<td>2%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>77%–87%</td>
<td>−6.56</td>
<td>60%–67%</td>
<td>25%–30%</td>
<td>22%–27%</td>
<td>21%</td>
<td>64.7%</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>68%</td>
<td>Not reported</td>
<td>76%</td>
<td>21%</td>
<td>32%</td>
<td>74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>72%</td>
<td>−5.23</td>
<td>51%</td>
<td>6%</td>
<td>64%</td>
<td>64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>78%–94%</td>
<td>−5.22</td>
<td>90%–94%</td>
<td>9%</td>
<td>70%</td>
<td>70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>74.4%–100%</td>
<td>−5.5</td>
<td>85%–88%</td>
<td>3%</td>
<td>66.6%</td>
<td>66.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>76%</td>
<td>Not reported</td>
<td>93%</td>
<td>0%</td>
<td>0%</td>
<td>72%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction.
Entecavir resistance

One disadvantage of nucleos(t)ide analogs is development of antiviral resistance with prolonged use. Resistance is accompanied by virologic and biochemical breakthrough, and, in rare cases, hepatic decompensation and death. Rates of lamivudine resistance exceed 70% by year 4 of treatment, limiting its usefulness for first-line therapy. Resistance rates for adefovir and telbivudine are lower, yet still clinically significant (Figure 1). Tenofovir resistance has not yet been well defined but appears to be rare, as no signature mutation has been defined and genotypic resistance through 4 years of therapy has not been reported.

Resistance to HBV antivirals is conferred by mutations in the HBV polymerase, which render the agent ineffective. For lamivudine, the signature mutation is a change in the reverse transcriptase at position 204 from methionine to valine or isoleucine (rtM204V/I). The rtM204I mutation also confers resistance to telbivudine. Lamivudine-resistant patients may develop a compensatory mutation at position 180 from leucine to methionine (rtL180M), which restores viral fitness. Adefovir does not show cross-resistance with lamivudine or telbivudine, with its signature resistance mutations a change from asparagine to threonine at position 236 (rtN236T) or alanine to valine or threonine at position 181 (rtA181V/T).

Entecavir resistance is unique because it requires up to three mutations for full resistance to develop. The rtM204V/I mutation, lamivudine’s signature mutation, is necessary but not sufficient for entecavir resistance, causing an 8- to 10-fold decrease in susceptibility to entecavir compared with wild-type HBV. Additional mutations at positions rtI169, rtT184, rtS202, and rtM250 confer additional decreases in entecavir susceptibility. These mutations alone have only a minimal impact on entecavir efficacy, but in the presence of an rtM204 mutation, the addition of one of these mutations leads to a 10- to 250-fold decrease in entecavir susceptibility and two mutations to a 500- to 1000-fold decrease.

The large genetic barrier to resistance has predictably led to low observed rates of clinical genotypic entecavir resistance in trials of nucleos(t)ide-naïve HBV patients. In the registration trials of entecavir, rates of genotypic resistance after 1 year were 0% in both HBeAg-positive and HBeAg-negative patients. A long-term resistance cohort from these trials has demonstrated that, after 4 years, cumulative resistance in naïve patients was 0.8% and, after 6 years, 1.2%. Cumulative genotypic resistance rates among lamivudine-refractory patients are much higher: 6%, 15%, 36%, 47%, 51%, and 57% at years 1–6, respectively. Although entecavir has been studied in lamivudine-refractory patients, its use as a salvage drug in this setting is generally not recommended when other options are available, because of these higher resistance rates. This demonstrates the superiority of entecavir when used as a first-line agent rather than following lamivudine failure, and highlights the importance of considering antiviral sequencing when selecting initial HBV therapy.

Special populations

Advanced fibrosis, cirrhosis, and transplanted patients

Approximately 15% of the subjects enrolled in the registration trials of entecavir had advanced fibrosis, defined as
Infection and Drug Resistance downloaded from https://www.dovepress.com/ by 54.70.40.11 on 08-Apr-2019
For personal use only.

an Ishak score of 4–6. All patients had compensated liver disease. Results in this subgroup of patients were published separately.48 For all endpoints examined in the parent studies, subjects with advanced fibrosis achieved comparable efficacy with the overall study population, including HBeAg-positive, HBeAg-negative, and lamivudine-refractory populations. Up to 59% of patients experienced an improvement in Ishak fibrosis score, which was better than that seen in the study population at large. Patients with advanced fibrosis or cirrhosis did not experience any more adverse events than the overall study population. No patient discontinued entecavir due to adverse events. There was a single ALT flare in the entecavir group. All deaths in the entecavir arm during the trial occurred in the subgroup with advanced fibrosis or cirrhosis, but no death was deemed related to study drug. One patient died from a gastrointestinal bleed secondary to a splenic lymphoma, one from hepatocellular carcinoma, and one from multiorgan failure from diabetes mellitus and cirrhosis.48

Experience with entecavir in decompensated cirrhosis has shown improvements in Child–Turcotte–Pugh (CTP) scores (from 8.1 to 6.6) and Model for End-stage Liver Disease (MELD) scores (from 11.1 to 8.8) after 1 year of therapy.49 In this single-center study, all patients were nucleos(t)ide naïve, as well as naïve to interferon. Compared with patients with compensated liver disease, those with decompensated cirrhosis had comparable rates of undetectable HBV DNA at month 12 (89.1% versus 78.5%, P = 0.104), HBeAg seroconversion (22.2% versus 24.4%, P = 0.812), HBeAg loss (48.1% versus 41.1%, P = 0.512), and ALT normalization (76.4% versus 75.0%, P = 0.535).49 There were no virologic breakthroughs on therapy. The cumulative incidence of mortality was 17% and the cumulative incidence of HCC or liver transplant was 6.9% among the decompensated cirrhotics, but no control group was reported.

Entecavir has also been compared with adefovir in a Phase IIIb study in subjects with evidence of hepatic decompensation.50 At baseline, the mean HBV DNA in the entecavir group was 7.53 log copies/mL, mean MELD 17.1, and mean CTP score 8.81. Thirty-six percent of subjects were lamivudine resistant, and 54% were HBeAg positive. In an interim analysis of the first 100 patients to complete 96 weeks of treatment, entecavir had a statistically significant higher rate of HBV DNA < 300 copies/mL at week 48 compared with adefovir (57% versus 20%, respectively, P < 0.0001). Entecavir also had higher rates of ALT normalization (63% versus 46%, P = 0.0425) at week 48. Rates of HBeAg loss (11% versus 18%), HBeAg seroconversion (6% versus 10%), and HBsAg loss (5% versus 0%) were not statistically different. As shown in the prior study, MELD scores improved by −2.6 in the entecavir group. Thirty-five percent of entecavir-treated patients had a reduction in their CTP score by two or more points at week 48. Serious adverse events occurred in over 65% of both treatment groups, but the details of these events were not reported. Adverse events led to drug discontinuation in 7% of entecavir patients and 6% of adefovir patients. Further follow-up of these patients is needed to determine the effects of antivirals on patients’ mortality and development of HCC. Although no major events were reported in these trials of entecavir in decompensated patients, caution is advised with its use in these fragile patients, as later case reports demonstrated fatal lactic acidosis.

There is little published information on entecavir in the post-liver transplant population. A single-center retrospective case-control study of 30 patients treated with entecavir compared with lamivudine showed that entecavir achieved undetectable HBsAg levels earlier than lamivudine (median 3 days versus 5 days).51 There were fewer HBV recurrences in the entecavir group (0% versus 11.1% in the lamivudine group), but cumulative survival rates after 30 months were similar in both groups (actuarial survival 81%). Larger, prospective trials are needed in this population, but the limited data available are favorable. Given the long-term therapy necessary post-transplant, the low resistance rates associated with entecavir make it an attractive option for post-transplantation prophylaxis.

HIV
Entecavir has been studied in HIV-positive patients failing lamivudine-containing antiretroviral regimens.52 Ninety-five percent of these patients had lamivudine resistance at baseline, and the 1 mg dose of entecavir was used. At 48 weeks, HBV DNA decreased by 4.2 log copies/mL, and 8% of subjects had an undetectable HBV DNA. ALT normalization occurred in 37%, and only 2% achieved HBeAg loss/HBeAg seroconversion.

During clinical development, entecavir was not shown to have any activity against HIV. It therefore became the treatment of choice for HIV patients requiring treatment of HBV who did not meet criteria for antiretroviral therapy for HIV. Following its approval, reports of entecavir’s effects on HIV replication and resistance were reported.53,54 In these reports, entecavir decreased HIV viral loads by about 1 log copies/mL. More sensitive in vitro assays using primary CD4+ T cells rather than transformed cell lines confirmed entecavir
inhibition of HIV in the low nanomolar range.\textsuperscript{53} In addition to effects on HIV viral load, entecavir also selected for the methionine to valine mutation at position 184 (M184V) of the HIV reverse transcriptase, which is the signature mutation for HIV resistance to lamivudine. This occurred in three patients in the absence of any exposure to antiretrovirals.\textsuperscript{54} Because of these reports, entecavir is not recommended as monotherapy in HIV/HBV coinfection for antiretroviral therapy in HIV patients, regardless of CD4 count or HIV viral load. This recommendation stems in part from the HIV treatment guidelines from the United States Department of Health and Human Services\textsuperscript{55} and the International AIDS Society-USA\textsuperscript{55,56} list active chronic HBV as an indication for antiretroviral therapy in HIV patients, regardless of CD4 count or HIV viral load. This recommendation stems in part from these findings related to entecavir activity.

**Adverse effects**

During the Phase III trials of entecavir, there were no adverse effects of the drug that occurred more often than with the comparator drug. The most common adverse events were elevations in ALT, which were associated in all cases with reductions in HBV DNA.\textsuperscript{12,13} In most cases, these were self-limiting with continued treatment with entecavir. Among nucleoside-naïve HBeAg-positive patients, ALT flares over twice baseline and >10 times upper limit of normal (ULN) occurred in 3\% of entecavir-treated patients, and ALT flares over twice baseline and more than five times ULN occurred in 10\% of subjects.\textsuperscript{12} These numbers in naïve HBeAg- negative subjects were <1\% and 2\%, respectively.\textsuperscript{13} Discontinuation due to adverse events was 2\% or less in both studies at 1 year. There were no unusual adverse effects during the Phase II and III trials that were concerning.

Experience with nucleoside analogs in the treatment of HIV demonstrated an association with certain drugs and lactic acidosis variably accompanied by hepatic steatosis, pancreatitis, peripheral neuropathy, and myopathy. The deoxy-nucleotide analogs were particularly implicated (didanosine [ddI], zalcitabine [ddC]). Development of an investigational drug for HBV, fialuridine (FIAU), was halted after seven patients in a Phase II trial developed severe lactic acidosis after a minimum of 9 weeks of therapy.\textsuperscript{57} Five patients in the study died, and two survived only after emergent liver transplant. All seven had pancreatitis with severe lactic acidosis and hepatic failure. Histologic examination showed marked macro- and microvesicular steatosis and cholestasis. Mitochondrial anatomy was distinctly abnormal on electron microscopy. In part because of these clinical reports, all nucleos(t)ide analogs, including entecavir, carry a black-box warning against the occurrence of lactic acidosis and severe hepatomegaly with steatosis.

Further study into the mechanisms for both HIV antiretroviral and FIAU toxicity implicate damage to mitochondria as the reason for metabolic perturbation.\textsuperscript{58–60} In addition to inhibition of the viral polymerase, nucleoside analogs also inhibit the polymerase function of the human DNA polymerase-γ, which is responsible for replication of mitochondrial DNA.\textsuperscript{60} Depletion of mitochondrial DNA leads to mitochondrial dysfunction, as synthesis of proteins essential for oxidative phosphorylation is inhibited. Mutations in mitochondrial DNA and oxidative stress within the mitochondria may also contribute to this dysfunction. Electron leakage from the electron transport chain occurs with disruption of oxidative phosphorylation, increasing production of reactive oxygen species.\textsuperscript{60}

In vitro studies of entecavir did not show any evidence for mitochondrial toxicity.\textsuperscript{61} Incubation of hepatoma HepG2 cells with entecavir at 10 times maximum concentration produced no nonspecific cell cytotoxicity. Entecavir also did not affect extracellular lactate levels at the highest concentrations and durations tested. In assays of mitochondrial DNA, levels were not decreased on exposure to entecavir when compared with controls. Even at 100 times achievable concentrations in vivo, there were no changes in mitochondrial protein levels. Assays to assess DNA polymerase-γ showed that entecavir did not utilize or inhibit function.

Despite these in vitro studies, postmarketing case reports of severe lactic acidosis during treatment with entecavir were published.\textsuperscript{62,63} In the first report, entecavir was used in combination with adefovir to treat a newly recognized HBV patient who developed a severe flare of hepatitis following chemotherapy for chronic lymphocytic leukemia.\textsuperscript{64} At the time of treatment initiation, his MELD score was approximately 24. His ALT was 3521 U/L, AST 2853 U/L, and bilirubin 20.9 mg/dL. After 10 days of combination therapy, he presented with dyspnea, hypoxia, and profound metabolic acidosis. With a lactate level of 9.5 mEq/L, pH 6.95, and carbon dioxide level 8 mmol/L. Entecavir and adefovir were discontinued. Despite aggressive measures, the patient expired within 24 hours of admission.

A second report describes a case series of 16 patients with advanced liver disease/decompensated cirrhosis treated with entecavir, of whom five developed lactic acidosis.\textsuperscript{62} In three cases, the syndrome was severe, and one of these cases died. Of the severe cases, lactic acidosis developed at 5 days, 8 days, and 8 months after initiation of entecavir. One of these cases was a post-liver transplant patient with
In some cases, lamivudine remains a first-line option in this setting. For patients who already express lamivudine resistance, entecavir is not the optimal salvage drug, as entecavir resistance develops more quickly. Telbivudine is also cross-resistant, and patients failing this drug are also not good entecavir candidates. For patients failing lamivudine or telbivudine, tenofovir is a better alternative. For failures of adefovir or tenofovir, entecavir is predicted to maintain full activity and is a reasonable salvage choice.

Summary

The approval of entecavir in 2005 began a new era in the treatment of HBV where long-term virologic suppression was both realistic and safe. The low risk of entecavir resistance in naïve patients, in part due to its rapid and potent suppression of HBV DNA, makes it an optimal choice for the initial therapy of both HBeAg-positive and HBeAg-negative patients. It requires three mutations to develop full resistance, the first of which is selected by lamivudine; hence, its activity is reduced in patients with genotypic lamivudine resistance. This is partly overcome by the use of a larger dose in lamivudine-refractory patients. There are few adverse effects associated with entecavir, although fatal cases of lactic acidosis have been reported with its use in decompensated cirrhosis, particularly when the MELD score exceeds 22. It should be used with caution in this population. Its efficacy in HIV/HBV coinfected patients has been established, although it should not be used without a fully suppressive antiretroviral regimen, as anti-HIV activity has been described in vitro and in vivo. Its impact on end-stage liver disease and mortality has yet to be delineated, as it is yet too early to see the benefits of long-term viral suppression.

Disclosure

The author reports no conflicts of interest in this work.

References


