Adefovir Dipivoxil: A New Agent For Active Hepatitis B Virus Infection

Tarrah Williams, PharmD Candidate, Marlon Honeywell, PharmD, Evans Branch III, PharmD, and Frank Emanuel, PharmD

INTRODUCTION

The leading cause of cirrhosis and hepatocellular carcinoma around the world is chronic hepatitis B virus (HBV) infection. Approximately 10% of patients who carry the human immunodeficiency virus (HIV) in the U.S. are co-infected with HBV and face decreased survival rates. Worldwide, 400 million people are chronically infected with hepatitis B.

Interferon alfa-2b (Intron® A, Schering) and lamivudine (Epivir-HBV®, GlaxoSmithKline) have been approved by the Food and Drug Administration (FDA) for the treatment of chronic HBV infection. Fewer than 50% of the patients with chronic HBV, however, are candidates for interferon alfa-2b, and this therapeutic option has shown only modest success. Among co-infected patients, lamivudine resistance develops in about 24% of patients after one year of therapy, in 47% after two years of therapy, and in 67% after four years of therapy.

The limited number of approved agents for the treatment of chronic HBV infection and the increase in the number of patients co-infected with HIV and HBV have reinforced the need for safe and effective new therapies. On September 20, 2002, the FDA approved the nucleotide reverse transcriptase inhibitor (NRTI) adefovir dipivoxil (Hepsera™, Gilead). Although this drug had previously been considered for the treatment of HIV, at higher dosing levels it was found to be associated with significant renal disease. At lower—and apparently safer—doses, adefovir has proved to be effective in the treatment of HBV in mono-infected patients, in HIV/HBV co-infected patients, and in lamivudine-resistant co-infected patients.

PHARMACOLOGY

Hepsera™ is a diester prodrug of adefovir, which is an acyclic nucleotide analogue of adenosine monophosphate. Through cellular kinases, adefovir is phosphorylated to the active metabolite, adefovir diposphosphate. Adefovir diposphosphate inhibits HBV deoxyribonucleic acid (DNA) polymerase by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA.

Up to week 48, studies have shown no mutations in the HBV DNA polymerase gene that might grant reduced vulnerability to adefovir. As a result of the lack of data showing a resistance to adefovir, its efficacy has been found to be greater than that of lamivudine.

PHARMACOKINETICS

From a 10-mg single dose of Hepsera™, the approximate bioavailability of adefovir is 98%. After oral administration of a 10-mg single dose of Hepsera™ to patients with chronic hepatitis B, the peak adefovir plasma concentration has been 18.4 ± 6.26 ng/ml, occurring between 0.58 and 4.00 hours after a dose. The adefovir area under the plasma concentration-time curve is 220 ± 70.0 ng • hour/ml. Plasma adefovir concentrations decline in a biexponential manner, with a terminal elimination half-life of 7.48 ± 1.65 hours.

Adefovir dipivoxil is rapidly converted to adefovir after oral administration. Following a 10-mg dose of Hepsera™, 45% of the dose is recovered as adefovir in the urine over 24 hours at a steady state. It is excreted renally by a combination of glomerular filtration and active tubular secretion.

Following a 10-mg dose of Hepsera™, the pharmacokinetics of adefovir varies in patients with moderately or severely impaired renal function or with end-stage renal disease (ESRD) and who need hemodialysis. For these patients, the plasma concentration, the area under the plasma-time curve, and the half-life are greater than in patients with normal renal function.

The recommended dosage and dosing interval adjustments for patients with renal impairment are listed in Table 1. The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. In addition, these guidelines were derived from data in patients with pre-existing renal impairment at baseline values and might not be appropriate for patients in whom renal insufficiency evolves during treatment.

Efficacy

The Marcellin Trial

Marcellin et al. evaluated the safety and efficacy of adefovir dipivoxil (10 mg and 30 mg), once daily, compared with placebo in a two-year trial (study 437) of 515 patients. These patients had hepatitis B early antigen (HBeAg) with chronic HBV infection, and the median age was 33 years. During the first 48 weeks of...
the study, 172 patients received adefovir dipivoxil 10 mg, 173 received adefovir dipivoxil 30 mg, and 170 received placebo. Although the 30-mg dose of adefovir dipivoxil had greater efficacy than the 10-mg dose, it showed increased toxicity. It was necessary to reduce the dose in 25% of the patients taking the 30-mg dose; a dose reduction was warranted in only 3% of those taking the 10-mg dose.6

These study results demonstrated that higher baseline alanine aminotransferase (ALT) values are associated with significant increases in histological improvement and HBeAg seroconversion (Table 2).2 Continued treatment with adefovir dipivoxil 10 mg once daily for 72 weeks resulted in continued maintenance of mean reductions in the serum HBV DNA observed at week 48.8

### The Hadziyannis Trial
An ongoing clinical trial (study 438), conducted by Hadziyannis et al.,9 has enrolled 185 patients with pre-core mutant HBV (HBeAg-negative, anti–HBe-positive, and HBV-DNA-positive). The median age of these patients is 46 years. Patients were randomly assigned to receive adefovir dipivoxil 10 mg once a day (n = 123) or placebo (n = 62) for 48 weeks. Following the first 48 weeks of treatment, the patients who had received adefovir dipivoxil were randomly reassigned (2:1) to receive either adefovir dipivoxil 10 mg or placebo for a second year. Patients who had initially received placebo have now been receiving adefovir dipivoxil 10 mg for the second 48 weeks of the study. Detailed results are presented in Table 3, and results from Kaplan-Meier estimates beyond 48 weeks are presented in Table 4.

### The Benhamou Study
Benhamou and colleagues10 assessed the safety and efficacy of adefovir 10 mg once daily in 35 patients co-infected with HIV and HBV (mean age, 41 years). Four patients withdrew early, two for adverse events (diabetes mellitus and insomnia), one for poor compliance, and one for personal reasons. The patients had controlled HIV ribonucleic acid (RNA), adequate renal function, and detectable HBV DNA despite Epivir-HBV® therapy. Adefovir 10 mg daily was added to the existing anti-HIV therapeutic regimen. Changes to treatment regimens were permitted, and all patients continued to take Epivir-HBV®. The patients were seen monthly for safety and efficacy evaluations.

In this ongoing study, the use of adefovir 10 mg once daily, when added to Epivir-HBV® for 88 weeks, resulted in continued significant antiviral activity against Epivir-HBV®-resistant HBV. Twelve percent of the co-infected patients experienced histological improvement and HBeAg seroconversion. No adefovir-related HBV or HIV mutations occurred, and there was no any laboratory or clinical evidence of nephrotoxicity.11

### ADVERSE REACTIONS
Table 5 lists all treatment-related clinical adverse events that occurred in 3% or more of the Hepsera™-treated patients compared with those receiving placebo. Increased asthenia, headache, and abdominal pain are the most frequently reported adverse events, followed by nausea and flatulence. Two other less commonly reported side effects are diarrhea and dyspepsia.
CONTRAINDICATIONS AND PRECAUTIONS

Hepsera™ is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with this drug. In clinical trials of Hepsera™, exacerbations of hepatitis occurred in up to 25% of patients after discontinuation of therapy, with most of these events occurring within 12 weeks of discontinuation. Although most of the adverse events were resolved with re-initiation of treatment, severe hepatitis exacerbations and fatalities have been reported. Therefore, patients who discontinue drug therapy should be closely monitored for hepatic function at repeated intervals over a period of time.

PREGNANCY AND LACTATION

No data are available regarding the use of adefovir in pregnant patients; there are no data on whether it is excreted in breast milk. The drug should be used during pregnancy only if it is clearly needed and only after careful consideration of the risks and benefits. Mothers should be instructed not to breast-feed while they are taking Hepsera™.

CONCLUSION

It is expected that Hepsera™ will be used to treat adults with chronic HBV infection, patients with HIV/HBV co-infection, and patients with lamivudine resistance. The recommended dose in patients with chronic hepatitis B and with adequate renal function is 10 mg, once daily, taken orally. The optimal duration of treatment is unknown. Hepsera™ appears to offer a significant alternative to other HBV agents that are associated with high resistance. Resistance to Hepsera™ has not yet been documented, and it appears to be a potentially viable agent against HBV infection.

REFERENCES


Table 3 Comparison of Adefovir Dipivoxil (ADV) 10 mg Once Daily with Placebo After 48 Weeks of Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADV (n = 123)</th>
<th>Placebo (n = 61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology improvement</td>
<td>64%</td>
<td>33%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Necroinflammatory improvement</td>
<td>80%</td>
<td>42%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Necroinflammatory worsening</td>
<td>3%</td>
<td>51%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fibrosis improvement</td>
<td>48%</td>
<td>25%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Fibrosis worsening</td>
<td>4%</td>
<td>38%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median reduction in HBV DNA</td>
<td>–3.91 (log_{10} copies/ml)†</td>
<td>–1.35 (log_{10} copies/ml)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/ml</td>
<td>51%</td>
<td>0%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median reduction in ALT levels (IU/liter)</td>
<td>–55</td>
<td>–38</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Percentage of patients achieving normal ALT levels</td>
<td>72%</td>
<td>29%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Table 4 Efficacy of Adefovir Dipivoxil 10 mg Once Daily Beyond 48 Weeks (Studies 437 and 438)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 437 (n = 309)</th>
<th>Study 438 (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48</td>
<td>Week 72</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/ml*</td>
<td>26%</td>
<td>46%</td>
</tr>
<tr>
<td>ALT normalization*</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>HBeAg loss*</td>
<td>23%</td>
<td>44%</td>
</tr>
<tr>
<td>HBeAg seroconversion*</td>
<td>14%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Table 5 Treatment-Related Adverse Events Reported in 3% or More of All Patients Given Adefovir Dipivoxil (ADV) in Pooled Studies 437 and 438 (0–48 Weeks)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADV 10 mg (n = 294)</th>
<th>Placebo (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Improvement in the Kneel score of at least 2 points or greater and no worsening of the Knodell fibrosis score.
†Roche Amplicor Monitor® Test (PCR [polymerase chain reaction]).
ALT = alanine aminotransferase; HBV = hepatitis B virus; DNA = deoxyribonucleic acid; IU = International Units.

Kaplan-Meier estimates for all patients who completed 48 and 72 weeks of treatment.
ALT = alanine aminotransferase; DNA = deoxyribonucleic acid; HBeAg = hepatitis B early antigen; HBV = hepatitis B virus.
Data from Brosgrat C. Oral presentation at the Food and Drug Administration Antiviral Advisory Committee Meeting, August 6, 2002.
DRUG FORECAST


8. Brosart C. Adefovir dipivoxil 10 mg for the treatment of chronic hepatitis B. Oral presentation at the FDA Antiviral Advisory Committee Meeting, August 6, 2002.


REFERENCES


CE and CME Articles

Beginning in 2003, selected articles will be approved for both CE and CME credit. They will appear in P&T every other month, starting with the February issue, so you will have more opportunities to get continuing education credits. Readers are encouraged to submit articles that they think are appropriate for CE and CME accreditation. Articles that are to be considered for dual accreditation should provide an overview of topics that are directly relevant to health care practitioners and should address issues such as disease management, drug class reviews, strategies for coping with medication errors, and pharmacoeconomic issues. They should cover topics of broad interest and contain appropriate references and up-to-date studies. Manuscripts that meet these criteria will be put on a faster track for publication than "regular" articles. Please contact the editor if you have questions about an article’s suitability for CE/CME credit.

EDITORIAL

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There might be additional positive effects from such a refreshingly straightforward idea. For example, people might recognize that they are not always getting the quality of care that they have paid for and that they had assumed to be good care. Here is where David’s work over the last seven years comes to the fore. FACCT’s mission, in part, is to help the public recognize that it may not be getting the value for its health care dollar. In addition, such a statutory support for error reporting would help us turn those errors into gold, literally, by improving the process, by weeding out poor performers, and by ensuring that Medicare beneficiaries get the right drug at the right dose, at the right time, by the right route, and for the right patient—the “five rights” that were discussed in the October 2002 issue of P&T.

Sometimes great ideas appear deceptively simple-minded. Of course, there are organizational and political barriers that we have not considered, such as requiring the Secretary of Health and Human Services to establish reporting specifications within 12 months of enactment, based on consultation with appropriate private and public sector experts and organizations. This is surely a tall order for our regulatory bodies, but it is doable, in my view.

Instead of continuing the debate about medical errors and the public hand-wringing and brow-furrowing that they entail, let us work together to implement effective legislation to turn errors into gold and to redistribute that “gold” in the form of a Medicare drug benefit for millions of deserving Americans.

I believe that David Lansky is onto something; I would like to hear your views as well. As usual, you can write to me, at david.nash@mail.tju.edu, or to FACCT.3

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