Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis with Telbivudine or Adefovir

A Randomized Trial

Henry L.Y. Chan, MD; E. Jenny Heathcote, MD; Patrick Marcellin, MD; Ching-Lung Lai, MD; Mong Cho, MD; Young M. Moon, MD; You-Chen Chao, MD; Robert P. Myers, MD; Gerald Y. Minuk, MD; Lennox Jeffers, MD; William Sievert, MD; Natalie Bzowej, MD, PhD; George Harb, MD; Ralf Kaiser, PhD; Xin-Jian Qiao, ScD; Nathaniel A. Brown, MD; and the 018 Study Group*

Background: The efficacy of nucleoside and nucleotide analogues for hepatitis B has been linked to the magnitude and durability of hepatitis B virus (HBV) suppression.

Objective: To compare the antiviral efficacy of telbivudine and adefovir dipivoxil, and the effects of switching from adefovir to telbivudine, in hepatitis B e antigen (HBeAg)–positive patients with chronic hepatitis B.

Design: Randomized, controlled, open-label trial.

Setting: 16 outpatient clinics.

Patients: 135 treatment-naive, HBeAg-positive adults with chronic hepatitis B.

Intervention: Patients were randomly assigned in a 1:1:1 ratio to 52 weeks of telbivudine (group A) or adefovir (group B), or 24 weeks of adefovir and then telbivudine for the remaining 28 weeks (group C). One hundred thirty-one patients completed 52 weeks of treatment.

Measurements: The primary efficacy comparison was serum HBV DNA reduction at week 24, with a secondary comparison at week 52.

Results: At week 24, mean HBV DNA reduction was greater in group A than in pooled groups B and C (−6.30 vs. −4.97 log_{10} copies/mL; difference, −1.33 log_{10} copies/mL [95% CI, −1.99 to −0.66 log_{10} copies/mL]; P < 0.001), and more patients in group A were polymerase chain reaction–negative (39% vs. 12%; odds ratio, 4.46 [CI, 1.86 to 10.72]; P = 0.001). At week 52, the mean residual HBV DNA level was lower in group A and group C than in group B (3.01 log_{10} copies/mL [group A] and 3.02 log_{10} copies/mL [group C] vs. 4.00 log_{10} copies/mL [group B]; difference, −0.99 log_{10} copies/mL [CI, −1.67 to −0.32 log_{10} copies/mL] and −0.98 log_{10} copies/mL [CI, −1.64 to −0.32 log_{10} copies/mL]; P = 0.004). Adverse events were similar across groups; the most common were upper respiratory symptoms, headache, back pain, and diarrhea.

Limitations: The trial was open-label and was not of sufficient size or duration to compare clinical outcomes and long-term efficacy.

Conclusion: Telbivudine demonstrated greater and more consistent HBV DNA suppression than adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients who had received continuous telbivudine or were switched to telbivudine after 24 weeks than in those who received continuous adefovir.

For author affiliations, see end of text.

*For members of the 018 Study Group, see the Appendix (available at www.annals.org).
ClinicalTrials.gov registration number: NCT00115245.

In chronic hepatitis B virus (HBV) carriers, elevated serum HBV DNA levels have been associated with increased risk for end-stage complications, such as cirrhosis and hepatocellular carcinoma (1–4). Corresponding evidence supports the concept that antiviral therapy can ameliorate liver injury and reduce or delay the progression of cirrhosis and the incidence of hepatocellular carcinoma (5–9). Effectively maintained viral suppression has been correlated with these effects (5, 10). Recent studies further suggest that, with direct-acting anti-HBV nucleosides and nucleotides, therapeutic efficacy and the emergence of resistance are related to the degree of viral suppression achieved early in the course of treatment (11–18). Specifically, achieving low serum HBV DNA levels in the first 6 to 12 months—preferably levels undetectable by polymerase chain reaction (PCR) assay—has been associated with greater subsequent efficacy and less resistance, with observations now extending to treatment periods beyond 2 years. Maximizing early viral suppression is therefore emerging as an important therapeutic goal for patients with hepatitis B.

Telbivudine and adefovir are approved for use in the United States and elsewhere (8, 19–22). Telbivudine, a thymidine nucleoside analogue, had greater antiviral efficacy than lamivudine in phase IIb and III trials (22, 23). Adefovir, an adenosine nucleoside analogue, had greater efficacy than placebo in phase III trials (8, 21). Telbivudine and adefovir have not been compared directly, although HBV DNA reductions after 1 year of telbivudine in phase
III trials seemed greater than those reported with adefovir in similar patient populations (8, 21, 22).

We compared the degree of telbivudine- and adefovir-induced viral suppression after 24 and 52 weeks of treatment to assess the relative antiviral efficacy and safety of these agents. Because trial data (8, 22) suggest that the clinical antiviral effects of telbivudine may be greater than those of adefovir, we also assessed antiviral efficacy and safety in patients switched to telbivudine after receiving adefovir treatment for 24 weeks. Finally, we evaluated potential relationships between the degree of viral suppression achieved after 6 months of therapy and subsequent efficacy outcomes at 1 year.

Methods
Design Overview
In this open-label trial, we randomly assigned hepatitis B e antigen (HBeAg)–positive patients with chronic hepatitis B to receive telbivudine or adefovir for 52 weeks (groups A and B, respectively) or adefovir for 24 weeks and then telbivudine for the remaining 28 weeks of the study (group C), evaluating the results at weeks 24 and 52. Screening began on 21 October 2004, and the last patient’s last visit was on 16 August 2006. The study was conducted in compliance with the Declaration of Helsinki and in accordance with good clinical practice guidelines and applicable local regulations. All patients provided written informed consent, and all participating institutions received ethics committee approval. There was no data safety monitoring board.

Setting and Participants
We conducted this trial at 16 outpatient gastroenterology clinics at academic centers in Hong Kong, Australia, Canada, France, Korea, Singapore, Taiwan, Thailand, and the United States. Study investigators recruited participants from among their clinic patients after reviewing medical records and completing screening procedures to assess eligibility. Eligible patients were men or women with chronic hepatitis B 18 to 70 years of age, with no history or signs of hepatic decompensation, positivity for serum hepatitis B surface antigen (HBsAg), positivity for serum HBeAg, serum alanine aminotransferase (ALT) level between 1.3 and 10 times the upper limit of normal, and serum HBV DNA levels of at least $6 \log_{10}$ copies/mL. We excluded patients who were pregnant, breastfeeding, or coinfected with hepatitis C or D virus or HIV; had other known causes of liver disease, a history or signs of pancreatitis or hepatocellular carcinoma, or potentially confounding concomitant medical conditions; had ever been treated for hepatitis B with nucleoside or nucleotide analogues or had received interferon or other immunomodulatory agents within 12 months of screening; or had used alcohol or illicit drugs in the past 2 years. Patients with elevated serum creatinine levels, hemoglobin levels less than 110 g/L for men or less than 100 g/L for women, an absolute neutrophil count less than $2 \times 10^9$ cells/L, platelet counts less than $100 \times 10^9$ cells/L, $\alpha$-fetoprotein levels greater than $50 \mu$g/L, serum amylase or lipase levels at least 1.5 times the upper limit of normal, a prothrombin time prolonged by more than 3 seconds above the upper limit of normal, albumin levels less than 34 g/L, or total bilirubin levels at least 2 times the upper limit of normal were also excluded.

Randomization and Interventions
A centralized computer-generated process assigned eligible patients to each of the 3 treatment groups by using block randomization with block sizes of 3, implemented with an automated voice-response system. Eligible patients were randomly assigned in a 1:1:1 ratio to receive 600 mg (3 tablets) of telbivudine per day for 52 weeks (group A), 10 mg (1 tablet) of adefovir dipivoxil per day for 52 weeks (group B), or 10 mg of adefovir per day for 24 weeks followed by 600 mg of telbivudine per day for the remaining 28 weeks (group C). This design compared responses to telbivudine and adefovir at week 24, consistent with the primary study goal, and provided 3 treatment comparisons at week 52 (group A vs. group B vs. group C), as appropriate to secondary goals. Patients completing this study were offered enrollment in a follow-up study of continuing treatment with telbivudine if indicated.

Telbivudine was supplied by Idenix Pharmaceuticals, Cambridge, Massachusetts, and adefovir (Hepsera, Gilead Sciences, Foster City, California) was purchased commercially. The brittle nature of adefovir tablets precluded treatment blinding by routine overencapsulation. Investigators
were blinded to HBV serologic data from baseline until week 52.

Outcomes and Follow-up

Routine laboratory values, including HBV DNA levels, were obtained along with clinical status at screening; baseline; and weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52. Other HBV serologic markers were measured beginning at week 12. A central reference laboratory (Quintiles Transnational, Research Triangle Park, North Carolina) conducted all laboratory-based assessments (HBV markers, serum chemistries, hematology, and urinalyses). Staff at Quintiles Transnational collected clinical data and entered them into a database in accordance with standardized data management and quality assurance procedures. Adherence was evaluated at each study visit; evaluation methods included pill counts and discussions with study participants.

Outcomes and Measurements

Serum HBV DNA levels were assessed at each study visit by using the COBAS Amplicor PCR assay (Roche Molecular Systems, Branchburg, New Jersey), which has a lower limit of detection of 300 copies/mL. The primary treatment comparison was HBV DNA reduction from baseline values at week 24, with a secondary comparison at week 52. Other secondary efficacy measures included comparisons of mean residual HBV DNA levels, proportions of patients with HBV DNA who were PCR-negative or had HBV DNA values less than 5, 4, or 3 log_{10} copies/mL; serum ALT normalization; HBeAg loss and seroconversion; HBsAg loss and seroconversion; and primary treatment failure. Primary treatment failure was defined as completion of at least 24 weeks of treatment without achieving 2 consecutive serum HBV DNA values less than 5 log_{10} copies/mL, the minimal response threshold recommended by treatment guidelines when the study was designed (24, 25). After study completion, suboptimal response was defined for exploratory analyses as a serum HBV DNA level of 3 log_{10} copies/mL or greater at week 24, consistent with reports of greater resistance and poorer

---

**Figure 1. Study flow diagram.**

- **Assessed for eligibility (n = 208)**
- **Did not meet inclusion criteria (n = 72)**
  - ALT <1.3 times the upper limit of normal: 23
  - ALT >10 times the upper limit of normal: 12
  - HBV DNA <6 log_{10} copies/mL: 14
  - HBeAg negative: 12
  - Low absolute neutrophil count: 10
  - a-Fetoprotein >50 ng/mL: 6
  - Amylase >1.5 times the upper limit of normal: 5
  - Other criteria: 11

- **Randomly assigned (n = 136)**
  - **Telbivudine (n = 45)**
    - Allocated: 45
    - Received: 45
    - **Discontinued (n = 2)**
      - <24 wk: 0
      - ≥24 wk: 2 (1 pregnancy; 1 patient or investigator request)
    - **Analyzed**
      - Week 24: 45
      - Week 52: 43

  - **Adefovir (n = 45)**
    - Allocated: 45
    - Received: 44
    - Did not receive: 1 (patient withdrew consent)
    - **Discontinued (n = 2)**
      - <24 wk: 1 (nonadherence)
      - ≥24 wk: 1 (nonadherence)
    - **Analyzed**
      - Week 24: 43
      - Week 52: 42

  - **Adefovir 24 wk, then switched to telbivudine (n = 46)**
    - Allocated: 46
    - Received: 46
    - **Discontinued (n = 2)**
      - <24 wk: 1 (nonadherence)
      - ≥24 wk: 1 (nonadherence)
    - **Analyzed**
      - Week 24: 46
      - Week 52: 46

Primary exclusion criteria are listed; some patients met more than 1 exclusion criterion. One patient assigned to adefovir withdrew before initiation of treatment; thus, the intention-to-treat sample was 135 patients, of whom 45, 44, and 46 were assigned to receive telbivudine, adefovir, or adefovir for 24 weeks and then telbivudine for the remaining 28 weeks, respectively. One adefovir recipient withdrew before the week-24 analysis; 1 additional adefovir recipient and 2 telbivudine recipients withdrew before the week-52 analysis. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus.
efficacy outcomes for patients with this level of residual viremia (11, 17, 18).

Viral Breakthrough and Resistance

Viral breakthrough was defined as an on-treatment increase in HBV DNA over 2 consecutive determinations of greater than 1 log_{10} from nadir, or a single determination at week 52, consistent with recent recommendations (26, 27). Resistance (viral breakthrough with documented resistance mutations) was identified by PCR amplification of HBV DNA from sera of patients with viral breakthrough at week 52, followed by automated DNA sequencing of the entire 344-codon reverse transcriptase domain of the HBV polymerase gene at an independent reference laboratory (Delft Diagnostic Laboratory, Delft, the Netherlands).

Adverse Events

At all study visits, we evaluated clinical adverse events, regardless of drug attributability, and discontinuation of study treatment for any reason; confirmed serum creatinine level elevations of 44.2 µmol/L or greater (≥0.5 mg/dL) from baseline; and conducted graded assessments of laboratory abnormalities. Adverse event evaluations included spontaneous patient reports, open-ended questioning by the investigator, and physical examinations. They were documented on case report forms that included investigator assessments of possible cause and drug attributability. We used standard, recommended, open-ended questions to elicit adverse event information rather than checklists or targeted questionnaires. Staff at Quintiles Transnational monitored each study site at 6- to 8-week intervals to ensure complete data entry into case report forms, including adverse events, and to verify source data.

Statistical Analysis

With a target sample size of 120 patients and a 1:2 ratio of assignment to telbivudine or adefovir during the first 24 weeks, we estimated that our study had 98% power to detect a difference of 1.5 log_{10} copies/mL in HBV DNA reduction at week 24, the primary efficacy comparison.

This anticipated difference was based on previous clinical studies of these agents (8, 11). The analyses presented are based on data available at each time point, consistent with the low rate of patient discontinuation; no missing data were imputed. All end points and comparisons were predefined except for exploratory evaluations of suboptimal responders and relationships between week-24 viral load and subsequent efficacy responses. For continuous variables, such as HBV DNA reduction, we used analyses of variance to compare treatment results. For categorical variables, we used logistic regression; we present the odds ratios. Our exploratory analyses of relationships between viral load at week 24 and subsequent efficacy outcomes were based on the Fisher exact test. All analyses were tested at a 2-sided α level of 0.05. We analyzed the results at weeks 24 and 52 by using unadjusted models and models adjusted for baseline covariates (HBV DNA level, age, body mass index, sex, and study site). We analyzed data by using SAS for Windows, release 8.02 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

Idenix Pharmaceuticals and Novartis Pharmaceuticals provided funding for this study. The study protocol and statistical analysis plan were designed by the sponsors in conjunction with the academic investigators. The protocol was submitted to the U.S. Food and Drug Administration, and the study was conducted under an Investigational New Drug authorization from the U.S. Food and Drug Administration. Quintiles Transnational conducted data management and site monitoring and provided the study data to the study statistician, an employee of Idenix Pharmaceuticals, who completed preprogrammed data analyses.

RESULTS

Baseline Patient Characteristics

Of the 208 patients screened, 72 were excluded and 136 were enrolled (Figure 1). One patient assigned to

### Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telbivudine (Group A) (n = 45)</th>
<th>Adefovir (Group B) (n = 44)</th>
<th>Adefovir to Telbivudine (Group C) (n = 46)</th>
<th>Pooled Groups B and C (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>34 (18–60)</td>
<td>30 (19–47)</td>
<td>33 (18–53)</td>
<td>32 (18–53)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>35 (78)</td>
<td>40 (91)</td>
<td>27 (59)</td>
<td>67 (74)</td>
</tr>
<tr>
<td>Mean body weight (±SE), kg</td>
<td>68 ± 2.0</td>
<td>69 ± 1.8</td>
<td>63 ± 1.7</td>
<td>66 ± 1.3</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>35 (78)</td>
<td>39 (89)</td>
<td>43 (94)</td>
<td>82 (91)</td>
</tr>
<tr>
<td>Asian</td>
<td>42 (93)</td>
<td>39 (89)</td>
<td>43 (94)</td>
<td>82 (91)</td>
</tr>
<tr>
<td>White</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>4 (9)</td>
<td>2 (4)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Mean serum HBV DNA value (±SE), log_{10} copies/mL</td>
<td>9.57 ± 0.26</td>
<td>9.98 ± 0.23</td>
<td>9.47 ± 0.29</td>
<td>9.72 ± 0.19</td>
</tr>
<tr>
<td>Serum ALT level, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>133 (47–750)</td>
<td>144 (43–854)</td>
<td>110 (50–455)</td>
<td>119 (43–854)</td>
</tr>
<tr>
<td>Mean (±SE)</td>
<td>183 ± 23.6</td>
<td>199 ± 25.7</td>
<td>138 ± 12.8</td>
<td>168 ± 14.4</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; HBV = hepatitis B virus.
adeefovir withdrew before the start of treatment. Of the remaining 135 patients, 45 received telbivudine (group A), 44 received adefovir (group B), and 46 received adefovir for 24 weeks and then telbivudine for the remaining 28 weeks (group C). Adherence to study medication was considered good (≥80%) for at least 95% of patients in each treatment group at each study visit, and no unplanned crossovers occurred. Treatment groups were well matched at baseline for the primary analysis at week 24 (group A and pooled groups B and C) (Table 1). More than 90% of the enrolled patients were ethnically Asian, and baseline HBV DNA and ALT levels were similar across treatment groups.

Results at Week 24: Primary Treatment Comparison

We observed a consistent separation of mean serum HBV DNA levels according to treatment beginning at week 2 (Figure 2, top). At week 24, the reduction in mean serum HBV DNA level from baseline in group A differed from that in pooled groups B and C (–6.30 vs. –4.97 log10 copies/mL; difference, –1.33 log10 copies/mL [95% CI, –1.99 to –0.66 log10 copies/mL]; P < 0.001), as did the proportion of patients whose serum HBV DNA levels were undetectable by PCR (39% vs. 12%; odds ratio, 4.46 [CI, 1.86 to 10.72]; P = 0.001) (Table 2). Serum HBV DNA levels remained at or above 5 log10 copies/mL in more adefovir recipients than telbivudine recipients (42% vs. 5%; odds ratio, 0.07 [CI, 0.02 to 0.29]; P < 0.001).

Similarly, group A and pooled groups B and C differed in the proportions of patients with HBV DNA levels that remained at or above 3 log10 copies/mL (50% vs. 78%; P = 0.003) and 4 log10 copies/mL (32% vs. 61%; P = 0.003). Rates of ALT normalization were similar (Table 2). Comparisons of all week-24 results, adjusted for baseline covariates, generally concur with the unadjusted results.

Results at Week 52

In patients switched from adefovir to telbivudine at week 24 (group C), mean HBV DNA levels rapidly decreased by approximately 1.4 log10 copies/mL after week 24; within 8 weeks, they were nearly identical to levels in patients in group A (Figure 2, top). A corresponding increase in HBeAg seroconversion was evident in group C (Figure 2, bottom), although the differences were not statistically significant. At week 52, mean residual HBV DNA levels in groups A and C differed from those in group B (3.01 log10 copies/mL and 3.02 log10 copies/mL, respectively, vs. 4.00 log10 copies/mL; difference, –0.99 log10 copies/mL [CI, –1.67 to –0.32 log10 copies/mL] and –0.98 log10 copies/mL [CI, –1.64 to –0.32 log10 copies/mL]; P = 0.004) (Table 3). Reductions of mean serum HBV DNA levels were greater in groups A and C (–6.56 and –6.44 log10 copies/mL, respectively) than in group B (–5.99 log10 copies/mL; differences, –0.57 log10 copies/mL [CI, –1.41 to 0.27 log10 copies/mL] [P = 0.18] and –0.45 log10 copies/mL [CI, –1.28 to 0.38 log10 copies/mL] [P = 0.28]). These differences were statistically significant after adjustment for baseline covariates (Table 3). More patients in groups A and C than in group B were PCR-negative at week 52, although these differences did not reach statistical significance (60% and 54% vs. 40%; P = 0.07 and 0.20, respectively). The rate of primary treatment failure (HBV DNA levels remaining >5 log10 copies/mL through week 52) in group B (29%) also differed from that in group A (2%; odds ratio, 0.06 [CI, 0.01 to 0.48]; P = 0.008) and in group C (11%; odds ratio, 0.30 [CI, 0.10 to 0.96]; P = 0.042).

Loss of HBeAg was more common in group A than in pooled groups B and C at week 24, and was more common in groups A and C at week 52 (30% and 26%, respecti-
Treatment of Hepatitis B with Telbivudine or Adefovir

Table 2. Efficacy Results at Week 24 of Treatment*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Telbivudine (Group A) (n = 44)</th>
<th>Adefovir (Groups B and C) (n = 89)</th>
<th>Unadjusted Effect (95% CI)†</th>
<th>P Value</th>
<th>Adjusted Effect (95% CI)‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in mean HBV DNA level (≥5 log_{10} copies/mL)</td>
<td>−6.30 ± 0.21</td>
<td>−4.97 ± 0.21</td>
<td>−1.33 (~1.99 to −0.66)</td>
<td>&lt;0.001</td>
<td>−1.46 (~2.01 to −0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV DNA PCR-negative, %</td>
<td>39</td>
<td>12</td>
<td>4.46 (1.86 to 10.72)</td>
<td>0.001</td>
<td>6.03 (2.20 to 16.52)</td>
<td>0.001</td>
</tr>
<tr>
<td>HBV DNA level &gt;5 log_{10} copies/mL, %</td>
<td>5</td>
<td>42</td>
<td>0.07 (0.02 to 0.29)</td>
<td>&lt;0.001</td>
<td>0.07 (0.02 to 0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT normalization, %</td>
<td>58</td>
<td>61</td>
<td>0.89 (0.42 to 1.87)</td>
<td>0.76</td>
<td>0.91 (0.41 to 2.04)</td>
<td>0.83</td>
</tr>
<tr>
<td>Loss of HBeAg, %</td>
<td>16</td>
<td>11</td>
<td>1.48 (0.53 to 4.24)</td>
<td>0.45</td>
<td>1.81 (0.56 to 5.85)</td>
<td>0.32</td>
</tr>
<tr>
<td>HBeAg seroconversion, %</td>
<td>16</td>
<td>10</td>
<td>1.68 (0.58 to 4.86)</td>
<td>0.34</td>
<td>2.30 (0.69 to 7.70)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Summary statistics are presented for the 44 and 89 patients in the telbivudine and adefovir groups, respectively, with data available at week 24. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.
† For continuous variables, the difference in least-squares means is presented; for categorical response variables, the odds ratio is presented.
‡ Results adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site), on the basis of analysis of variance for continuous variables or logistic regression for categorical variables.

Table 3. Efficacy Results at Week 52 of Treatment*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Telbivudine (Group A)</th>
<th>Adefovir (Group B)</th>
<th>Adefovir to Telbivudine (Group C)</th>
<th>Unadjusted Effect (95% CI)†</th>
<th>P Value</th>
<th>Adjusted Effect (95% CI)‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in mean HBV DNA level, log_{10} copies/mL</td>
<td>−6.56</td>
<td>−5.99</td>
<td>−6.44</td>
<td>−0.57 (~1.41 to 0.27)</td>
<td>0.18</td>
<td>−0.84 (~1.49 to −0.19)</td>
<td>0.012</td>
</tr>
<tr>
<td>HBV DNA PCR-negative, %</td>
<td>60</td>
<td>40</td>
<td>54</td>
<td>2.25 (0.94 to 5.36)</td>
<td>0.067</td>
<td>1.89 (0.72 to 4.94)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean HBV DNA level, log_{10} copies/mL</td>
<td>3.01</td>
<td>4.00</td>
<td>3.02</td>
<td>−0.99 (~1.67 to −0.32)</td>
<td>0.004</td>
<td>−0.84 (~1.49 to −0.19)</td>
<td>0.012</td>
</tr>
<tr>
<td>ALT normalization, %</td>
<td>79</td>
<td>85</td>
<td>85</td>
<td>0.65 (0.21 to 2.02)</td>
<td>0.45</td>
<td>0.61 (0.18 to 2.08)</td>
<td>0.43</td>
</tr>
<tr>
<td>Loss of HBeAg, %</td>
<td>30</td>
<td>21</td>
<td>26</td>
<td>1.59 (0.59 to 4.25)</td>
<td>0.36</td>
<td>1.42 (0.50 to 4.07)</td>
<td>0.51</td>
</tr>
<tr>
<td>HBeAg seroconversion, %</td>
<td>28</td>
<td>19</td>
<td>24</td>
<td>1.65 (0.59 to 4.56)</td>
<td>0.34</td>
<td>1.49 (0.51 to 4.39)</td>
<td>0.47</td>
</tr>
<tr>
<td>Primary treatment failure, %</td>
<td>2</td>
<td>29</td>
<td>11</td>
<td>0.06 (0.01 to 0.48)</td>
<td>0.008</td>
<td>0.05 (0.0 to 0.45)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* Summary statistics are presented for the 43, 42, and 46 patients in the telbivudine, adefovir, and adefovir-to-telbivudine groups, respectively, with data available at week 52. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.
† For continuous variables, the difference in least-squares means is presented; for categorical response variables, the odds ratio is presented.
‡ Results adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site), on the basis of analysis of variance for continuous variables or logistic regression for categorical variables.

Relationship between Week-24 Viral Load and Week-52 Efficacy Responses

At week 24, serum HBV DNA levels were less than 3 log_{10} copies/mL in more patients in group A than in pooled groups B and C (50% vs. 22%; P < 0.001). Among patients who received 52 weeks of telbivudine or adefovir (groups A and B), those with HBV DNA level <3 log_{10} copies/mL at week 24 showed the highest rates of efficacy responses at week 52 (Table 4). In groups A and B combined, HBV DNA was undetectable at week 52 in 94% of patients with an HBV DNA level less than 3 log_{10} copies/mL at week 24, versus 25% of patients with a viral load of 3 log_{10} copies/mL or greater at week 24 (P < 0.001). Similarly, HBeAg seroconversion and ALT normalization at week 52 were observed in 44% and 94%, respectively, of patients with viral load <3 log_{10} copies/mL at week 24, compared with 11% and 75% of patients with HBV DNA levels of 3 log_{10} copies/mL or greater at week 24 (P = 0.001 and 0.04, respectively).
Viral Breakthrough and Resistance

Viral breakthrough, defined as a confirmed increase in serum HBV DNA levels of more than 1 log above the nadir value, occurred in 4 adefovir recipients and 3 telbivudine recipients. No breakthroughs occurred in the adefovir-to-telbivudine group. All breakthroughs occurred after week 24 in patients with serum HBV DNA levels that remained at $3 \log_{10}$ copies/mL or greater at week 24. No codon A181V/T or N236T signature resistance mutations were detected in adefovir recipients with viral breakthrough (27). The signature M204I telbivudine resistance mutation was detected at week 52 in the 3 telbivudine recipients with breakthrough; 1 of these was accompanied by an L80V secondary change (28).

In the study protocol, viral breakthrough was defined as an increase of serum HBV DNA to $5 \log_{10}$ copies/mL or greater after a decrease to below that level. During the study, this definition was superseded by the more widely accepted definition that pertains to the data reported here (27). Breakthrough per protocol occurred in 2, 1, and 0 patients in groups A, B, and C, respectively. All 3 patients were also included in the primary resistance analysis reported here.

Adverse Events

No drug-attributed serious adverse events were reported, no patients discontinued the study because of adverse events (1 patient withdrew after becoming pregnant), and no deaths occurred. Serious adverse events not attributed to study medications included a metacarpal fracture, transient elevation of ALT level, and hospitalizations for tonsillitis and a thyroid nodule. Clinical adverse events were similar in the 3 treatment groups (Table 5). Single cases of mild (grade 1) myopathy and persistent myalgia were detected in 2 adefovir recipients after 52 and 41 weeks, respectively; treatment with creatine kinase elevations were reported in telbivudine recipients (27). Breakthrough occurred in 4 adefovir recipients and 3 telbivudine recipients with breakthrough; 1 of these was accompanied by an L80V secondary change (28). The signature M204I telbivudine resistance mutation was detected at week 52 in the 3 telbivudine recipients with breakthrough; 1 of these was accompanied by an L80V secondary change (28).

In this study, telbivudine showed greater antiviral effects than adefovir dipivoxil after 24 weeks of treatment in HBeAg-positive patients with chronic hepatitis B. At week 24, 3 times as many telbivudine-treated patients (group A) as adefovir-treated patients (pooled groups B and C) were PCR-negative. Conversely, HBV DNA levels remained above $5 \log_{10}$ copies/mL in 42% of group B versus 5% of group A, suggesting more consistent antiviral suppression with telbivudine. Adefovir recipients randomly assigned to switch to telbivudine at week 24 (group C) showed a rapid, approximately 1-log incremental reduction of serum HBV DNA levels within 2 months. At 1 year, the difference in reduction of serum HBV DNA level, as assessed by residual HBV DNA levels, differed significantly when patients in groups A and C were compared with those in group B. Other measures at 1 year also consistently favored telbivudine over adefovir, although differences were not statistically significant. The incidence of viral breakthrough was similar for telbivudine and adefovir at 1 year, although resistance mutations were detected only with continuous telbivudine therapy (group A). Adverse event frequencies were similar in the 3 treatment groups; however, the occurrence of myopathy in a telbivudine recipient suggests that any persistent, unexplained muscle-related symptoms should be evaluated promptly.

Direct comparative studies are the most effective way to define the role of available agents for hepatitis B in clinical practice. A search of MEDLINE through March 2007 and hepatology conference abstracts from 2006 and 2007 identified several such studies. Phase III trials for both telbivudine and entecavir demonstrated greater antiviral efficacy at 1 year with less resistance (no resistance with entecavir) compared with lamivudine (9, 22, 23, 29, 30). A recent trial demonstrated greater antiviral effects with entecavir than with adefovir after 1 year (31).

Although all available agents have demonstrated greater antiviral efficacy than either placebo or lamivudine in phase III studies, a substantial proportion of patients receiving these agents did not achieve optimal viral suppression (7–9, 21, 29, 32). In a placebo-controlled, phase III study, the serum HBV DNA level was reduced by less than $2.2 \log_{10}$ copies/mL after 48 weeks in 25% of adefovir recipients (33). However, few studies have explored the effects of switching therapies as the basis for a rational strategy to improve efficacy outcomes. A small trial in

<table>
<thead>
<tr>
<th>Table 3—Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group C vs. Group B</strong></td>
</tr>
<tr>
<td>Unadjusted Effect (95% CI)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>$-0.45 (-1.28$ to $0.38)$</td>
</tr>
<tr>
<td>1.75 (0.75 to 4.08)</td>
</tr>
<tr>
<td>$-0.98 (-1.64$ to $-0.32)$</td>
</tr>
<tr>
<td>0.98 (0.30 to 2.31)</td>
</tr>
<tr>
<td>1.29 (0.48 to 3.48)</td>
</tr>
<tr>
<td>1.34 (0.48 to 3.73)</td>
</tr>
<tr>
<td>0.30 (0.10 to 0.96)</td>
</tr>
</tbody>
</table>

www.annals.org
HBeAg-negative patients with suboptimal response to adefovir showed enhanced antiviral effects after switching to a combination of tenofovir and emtricitabine (34). In lamivudine-resistant patients, several studies have shown that viral suppression can be restored by adding or switching to adefovir or tenofovir, nucleotide analogues with complementary resistance profiles (35–37). Related studies suggest that in lamivudine-resistant patients, tenofovir or a higher dosage of adefovir (20 mg/d) may provide greater viral suppression than standard adefovir treatment, with potential benefits for patients with suboptimal responses to adefovir salvage therapy (38, 39). However, adefovir dosages greater than 10 mg/d have been associated with a higher incidence of nephrotoxicity (8, 40).

Limitations of this study include an open-label design and reduced statistical power after the primary analysis at week 24, due to reduced group sizes associated with division of the study population into 3 comparator groups. In addition, the study was not of sufficient duration to evaluate long-term clinical outcomes. Because the patients were all HBeAg-positive and nucleoside- and nucleotide-naive and were primarily Asian, the extent to which conclusions may be generalized to other patient populations with hepatitis B is uncertain. The open-ended approach that was used to elicit adverse event information may have resulted in variable or incomplete reporting of events. In analysis of variance models, observations of nondetectable HBV DNA were handled by single-value imputation (150 copies/mL); consequently, any variability of actual values for these data may not be accurately reflected in variability estimates, confidence limits, and P values.

In this trial, we randomly assigned some adefovir recipients to switch to telbivudine at 24 weeks. In clinical practice, however, treatment modification is generally considered only for patients with suboptimal antiviral responses (41). Adefovir recipients with suboptimal antiviral responses at week 24 achieved a substantial incremental decrease in viral load after switching to telbivudine, suggesting that treatment modification can be considered as early as week 24. Recent studies (42, 43) suggest that adding adefovir to ongoing lamivudine therapy in patients with resistance may reduce subsequent adefovir resistance, compared with switching to adefovir monotherapy, and may improve viral suppression in patients with high viral load. The same advantages may also apply to patients without a resistant virus, although this has not been prospectively evaluated (44). The M204I and M204V mutations both confer resistance to lamivudine, whereas M204I is the primary basis of telbivudine resistance (28, 29). These mutations reduce susceptibility to other L-nucleoside analogues, but not to the acyclic phosphonates adefovir and tenofovir. These findings suggest that there may be benefits of combining telbivudine with these agents, analogous to those reported for lamivudine and adefovir (28). Studies are needed to refine the definition of suboptimal early response as a basis for therapeutic decisions, to confirm that the benefits of treatment modification persist in the long

<table>
<thead>
<tr>
<th>Event</th>
<th>Adefovir Group (n = 44)</th>
<th>Telbivudine Group (n = 45)</th>
<th>Adefovir-to-Telbivudine Group (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>64</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Back pain</td>
<td>13</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Influenza</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>7</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Malaise</td>
<td>7</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gastritis</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Toothache</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hordeolum</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

* Number of events occurring in ≥4% of patients in any treatment group through week 52, regardless of attributability to study drug. Patients are counted once for each type of adverse event.
Article

Treatment of Hepatitis B with Telbivudine or Adefovir

From The Chinese University of Hong Kong, Hong Kong, China; University of Toronto, Toronto, Ontario, Canada; Hôpital Beaujon, Clichy, France; Pusan National University Hospital, Busan, Korea; University of Toronto, Toronto, Ontario, Canada; Hoˆpital Beaujon, Clichy, France; Pusan National University Hospital, Busan, Korea; Severance University, Seoul, Korea; Tri-Service General Hospital, Taipei, Taiwan; University of Calgary, Calgary, Alberta, Canada; University of Manitoba, Winnipeg, Manitoba, Canada; University of Miami, Miami, Florida; Monash University, Melbourne, Victoria, Australia; California Pacific Medical Center, San Francisco, California; Novartis Pharmaceuticals, East Hanover, New Jersey; and Idenix Pharmaceuticals, Cambridge, Massachusetts.

Acknowledgment: The authors thank Drs. Raymond Koff and Richard Boehme for their assistance in the preparation of this manuscript.


Reproducible Research Statement: A synopsis of the protocol is available to interested readers by contacting 877-889-9352. Statistical code and data are not available.

Requests for Single Reprints: Henry L.Y. Chan, MD, The Chinese University of Hong Kong, 9/F Prince of Wales Hospital, Shatin, Hong Kong, China; e-mail, hlychan@cuhk.edu.hk.

Current author addresses and author contributions are available at www.annals.org.

References

2. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130:678-86. [PMID: 16539509]


**Current Author Addresses:**

Dr. Chan: The Chinese University of Hong Kong, 9/F Prince of Wales Hospital, Shatin, Hong Kong, China.

Dr. Heathcote: Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada.

Dr. Marcellin: Hôpital Beaujon, 100 Boulevard Général Leclerc, 92110 Clichy, France.

Dr. Lai: Department of Medicine, University of Hong Kong, 102 Pokfulam Road, Hong Kong, China.

Dr. Cho: Pusan National University Hospital, 1-10 Ami-dong Seo-gu, Busan, Korea, 602-739.

Dr. Moon: Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemun-Ku, Seoul, South Korea, 120-752.

Dr. Chao: Tri-Service General Hospital, Number 325, Sec. 2, Cheng-Kung Road, Taipei, Taiwan, 114.

Dr. Myers: Health Sciences Centre, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada.

Dr. Minuk: University of Manitoba, 715 McDermot Avenue, Winnipeg, Manitoba R3E 3P4, Canada.

Dr. Jeffers: University of Miami Center for Liver Diseases, 1500 NW 12th Avenue 1101, Miami, FL 33136.

Dr. Sievert: Monash Medical Center, Monash University, 246 Clayton Road, Melbourne, Victoria 3165, Australia.

Dr. Bzowej: California Pacific Medical Center, 2340 Clay Street, San Francisco, CA 94115.

Dr. Harb: Novartis, 1 Health Plaza, East Hanover, NJ 07936.

Drs. Kaiser, Qiao, and Brown: Idenix Pharmaceuticals, 1 Kendall Square, Cambridge, MA 02139.

**Author Contributions:**


Statistical expertise: X.J. Qiao.

Administrative, technical, or logistic support: R. Kaiser, N.A. Brown.

Collection and assembly of data: G.Y. Minuk, N. Bzowej, N.A. Brown.

**APPENDIX: MEMBERS OF THE 018 STUDY GROUP**

In addition to the authors, investigators in this trial included Dr. Darrell Crawford, Princess Alexandra Hospital, Woolloomooloo, Queensland, Australia; Dr. Seng-Gee Lim, National University Hospital, Singapore; Dr. Anuchit Chutaputti, Phramongkutklao Hospital, Bangkok, Thailand; and Dr. Thierry Poynard, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.