Evolution of Therapy for Chronic Hepatitis B: Progressing from the Simple to the Complex

In the past decade, physicians treating chronic hepatitis B have gained the luxury of choice. The U.S. Food and Drug Administration has approved 6 drugs for treating chronic hepatitis B (listed in order of approval date): interferon-α2b, lamivudine, adefovir, entecavir, pegylated interferon-α2a, and telbivudine. The introduction of nucleoside and nucleotide analogues has revolutionized therapy for chronic hepatitis B. Unlike interferon, these agents are orally administered, well tolerated, safe, and very effective at suppressing hepatitis B virus (HBV) replication. They improve liver disease and reduce rates of liver transplantation and hepatocellular carcinoma. However, because viral replication usually resumes after treatment with nucleoside and nucleotide analogues is stopped, long-term, perhaps indefinite, administration is essential. Unfortunately, long-term treatment usually brings viral resistance to drugs and, consequently, loss of clinical response, occasional flares of hepatitis, and sometimes death.

The wider choice of antiviral agents has raised new questions: which ones to use, how long to use them, what constitute suitable end points, and when to change therapy. The ultimate goal of therapy is to prevent the long-term complications of chronic hepatitis B: cirrhosis, decompensated liver disease, and hepatocellular carcinoma. Unfortunately, these end points are impractical for clinical trials and for measuring success in individual patients. Instead, investigators use surrogate end points. They define response by several variables: virologic (undetectable HBV DNA by a sensitive polymerase chain reaction−based assay or loss of hepatitis B e antigen [HBeAg] or hepatitis B surface antigen [HBsAg]), biochemical (normalization of serum alanine aminotransferase [ALT] levels), and histologic (2-point decrease in the histologic activity index score with no worsening of fibrosis). The timing of response is also important and is described as initial, maintained (on therapy), or sustained (off therapy). By using these definitions, we can compare the efficacy of the approved agents.

However, these response definitions are imperfect. Achieving a response does not reliably predict long-term remission of chronic hepatitis B and therefore is not necessarily an indication to stop therapy. With few exceptions, researchers have not been able to define reliable end points of treatment. Historically, HBeAg loss was the primary therapeutic end point because patients who spontaneously cleared HBeAg achieved long-term remission. However, regardless of treatment, only 12% to 33% of patients achieve this end point, and the response to treatment with nucleoside or nucleotide analogues is often short-lived. Loss of HbsAg is the most desirable end point because it correlates strongly with remission, but it occurs in only 1% to 3% of patients treated with nucleoside or nucleotide analogues. Histologic response is the gold-standard indicator of disease severity, but it is hard to define this measure and impractical to do repeated liver biopsies to measure response. When to test for a response is also unclear, in part because sustained response off therapy is infrequent. Most industry-sponsored trials of nucleoside and nucleotide analogues have used response at 48 or 52 weeks on treatment (“maintained” response) as the end point for defining efficacy, largely because response rates off therapy after 48 to 52 weeks of treatment are very low.

In this issue, Chan and colleagues compared the antiviral efficacy of telbivudine and adefovir dipivoxil at 24 weeks of therapy. In addition, they evaluated the strategy of switching from adefovir to telbivudine at 24 weeks. The authors randomly assigned 135 HBeAg-positive patients with elevated ALT levels to 1 of 3 treatment groups: telbivudine, 600 mg/d for 52 weeks; adefovir, 10 mg/d for 52 weeks; or adefovir, 10 mg/d for 24 weeks, followed by telbivudine, 600 mg/d for 28 weeks. To compare the 2 drugs, the authors used the reduction in HBV DNA level at 24 weeks relative to baseline DNA level as the primary end point. The secondary end point was the reduction in DNA levels at 52 weeks among the 3 groups. At 24 weeks, telbivudine achieved better viral suppression than adefovir (−6.3 log10 copies/mL vs. −4.97 log10 copies/mL [30% vs. 12% of patients with undetectable HBV DNA], respectively; P < 0.001). However, at 52 weeks, patients who received telbivudine, adefovir, or both drugs had similar viral suppression relative to baseline in the unadjusted analysis (−6.56, −5.99 and −6.44 log10 copies/mL, respectively; P = 0.28), and a similar proportion among the groups had undetectable HBV DNA (60%, 40%, and 54%, respectively; P = 0.067).

The study results at 24 and 52 weeks underscore something important about when to assess response to treatment: The results at 24 weeks more accurately reflect an initial treatment response. It is an interim measure of efficacy rather than a treatment end point in a disease that usually requires long-term therapy. The week-24 results clearly show that telbivudine, an 1-nucleoside analogue, achieves better antiviral suppression, and they highlight one of the strengths of telbivudine: excellent potency. However, we know little about the development of viral resistance to telbivudine. In contrast, adefovir, an acyclic phosphonate nucleotide analogue, has a higher rate of primary nonresponse (defined as a failure to achieve a 1– to 2-log10 IU/mL decrease in HBV DNA level after 24 weeks) and a low rate of viral resistance. Chan and colleagues’ trial illustrates the different performance character-
istics of these 2 agents. Although telbivudine had advantages at week 24, the unadjusted analysis showed that by week 52, the 3 treatment groups had similar rates of HBV DNA suppression and patients who tested negative for HBV DNA. In addition, the 3 groups had similar unadjusted rates of ALT normalization and HBeAg loss or seroconversion. This pattern of results highlights the difficulty of interpreting results at 24 weeks and emphasizes the need to use long-term rates of maintained response (undetectable HBV DNA, normal ALT level, and histologic response during treatment) to evaluate efficacy. Outcomes should be measured at 48 or 52 weeks at a minimum, and 4- to 5-year data are preferable. In addition, investigators should report sustained response rates in patients who stop therapy. In this context, the purpose of testing at week 24 is not to determine efficacy but to detect treatment failure, which may be due to early development of resistance to antivirals, primary nonresponse, or poor adherence to therapy.

A second aim of Chan and colleagues’ study was to evaluate the benefit of switching therapy at 24 weeks. The best way to evaluate this strategy would be to randomly assign patients with a poor initial response to therapy to switching versus continuing the assigned agent. In this trial, whether to switch therapy was randomly determined before starting any treatment, which means that patients who were responding well to adefovir may have been unnecessarily switched to telbivudine. With this caveat in mind, the authors performed a post hoc analysis, identifying a subgroup of patients with a suboptimal response to adefovir (which they defined as an HBV DNA level $\geq 3 \log_{10}$ copies/mL at week 24), who may benefit from switching. This criterion is much less stringent than the usual definition of primary nonresponse (a 1– to 2–$\log_{10}$ IU/mL decrease from baseline at week 24). Although this post hoc, adjusted analysis seems to favor switching, it does not give us guidance about whether to switch therapy in a patient with HBV DNA level that has been persistently decreasing but is still above $3 \log_{10}$ IU/mL at week 24. A predefined prospective evaluation of this strategy and longer-term outcome data are needed to answer this question.

Chan and colleagues do not tell us what happened at the end of the 52-week trial. If therapy was stopped, it is important to provide the relapse rate among the 3 groups and information on whether any withdrawal flares, hepatic decompensation, or deaths occurred. Similarly, if patients continued therapy, it would be important to know how long HBV DNA levels remained suppressed and whether efficacy eventually declined as antiviral resistance developed. In almost every trial of nucleoside and nucleotide analogues, response has eventually plateaued and then declined over time because antiviral resistance has emerged (1). Moreover, in clinical practice, the decision to change therapy depends on many factors—not just HBV DNA levels. Decision criteria should also include the potency and resistance profile of the agents selected, pretreatment HBV DNA level, history of exposure to antivirals, severity of the underlying liver disease, need for rapid viral suppression, and presence of comorbid illnesses.

A final concern about switching therapy is that sequential monotherapy (that is, switching from monotherapy with one drug to another) runs the risk for accumulating mutants that may persist and affect future response to antivirals (18). For example, resistance to entecavir, the most potent of the approved anti-HBV agents, is significantly higher in patients in whom lamivudine-resistant mutants form less than 0.1% of the viral population (19, 20). The worst-case scenario is a patient who has

### Table. Response to Approved Antiviral Agents after 48 to 52 Weeks among Treatment-Naive Hepatitis B e Antigen–Positive Patients*

<table>
<thead>
<tr>
<th>Response Criterion</th>
<th>Standard Interferon-$\alpha$, 5 million U/d to 10 million U/d Twice Weekly (9)</th>
<th>Pegylated Interferon-$\alpha$2a, 180 $\mu$g Once Weekly (5)</th>
<th>Lamivudine, 100 mg/d (5, 10, 11)</th>
<th>Adefovir, 10 mg/d (12)</th>
<th>Entecavir, 0.5 mg/d (10)</th>
<th>Telbivudine, 600 mg/d (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA negative by PCR, %†</td>
<td>37</td>
<td>25</td>
<td>36 to 40</td>
<td>21</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Mean reduction in HBV DNA level, $\log_{10}$ copies/mL</td>
<td>–</td>
<td>–4.5</td>
<td>–5.4 to –5.8</td>
<td>–3.57</td>
<td>–6.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Loss of HBeAg, %</td>
<td>33</td>
<td>30</td>
<td>20 to 23</td>
<td>24</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>HBeAg seroconversion, %</td>
<td>–</td>
<td>27</td>
<td>18 to 20</td>
<td>12</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Loss of HBsAg, %</td>
<td>7.8</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ALT normalization, %</td>
<td>NA</td>
<td>39</td>
<td>62 to 77</td>
<td>48</td>
<td>68</td>
<td>77</td>
</tr>
<tr>
<td>Histologic improvement, %§</td>
<td>NA</td>
<td>38</td>
<td>66 to 62</td>
<td>73</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>Rate of resistance, %</td>
<td>NA</td>
<td>0</td>
<td>14 to 24</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = not available; PCR = polymerase chain reaction.
† Data are derived from studies in which lamivudine was compared with entecavir, pegylated interferon-$\alpha$2a, and telbivudine.
§ Defined as a 2-point improvement in necroinflammation with no worsening of fibrosis.
| As determined by biopsy performed 24 weeks after treatment discontinuation.
no treatment options left after prematurely cycling through every class of drug, ostensibly because of incomplete responses.

Although therapy has improved over the past decade and most patients with chronic hepatitis B respond to treatment, rates of sustained response and HBsAg loss remain poor. Therefore, we urgently need new drugs aimed at novel antiviral targets if we are to achieve HBsAg loss and successfully prevent and manage resistance. Until then, studies should focus on optimizing currently available drugs by finding the best regimen to treat chronic hepatitis B and the appropriate measures for changing or discontinuing therapy. Unfortunately, this study leaves us with more questions than answers.

Jordan J. Feld, MD
Marc G. Ghany, MD
Liver Diseases Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health
Bethesda, MD 20892-1800

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Requests for Single Reprints: Marc G. Ghany, MD, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10, Room 9B-16, 10 Center Drive, MSC 1800, Bethesda, MD 20892-1800; e-mail, marcg@intra.niddk.nih.gov.

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

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References
Current Author Addresses: Drs. Feld and Ghany: Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10, Room 9B-16, 10 Center Drive, MSC 1800, Bethesda, MD 20892-1800