Following closely on the heels of the approval of telbivudine (Tyzeka, Novartis/Idenix) on October 25, 2006, for the treatment of chronic hepatitis B, presentations at the meeting featured the agent’s benefits of two-year results from the international GLOBE trial. Telbivudine, a once-daily oral agent, suppresses hepatitis B virus (HBV) in adults with evidence of viral replication and evidence of either persistently elevated liver enzymes aspartate and alanine transaminases (ALT and AST) or histologically active disease.

Lai et al.
Telbivudine and lamivudine (Epivir-HBV, GlaxoSmithKline) were compared in chronic hepatitis B early antigen (HBeAg)–positive patients and HBeAg–negative patients. Ching-Lung Lai, MD, Professor of Medicine at the University of Hong Kong and lead investigator of the GLOBE study, confirmed that superior responses reported for telbivudine at one year were sustained during a longer follow-up period.

The GLOBE trial included 1,367 patients with chronic HBV infection. These patients were randomly assigned, in a 1:1 ratio, to receive telbivudine or lamivudine. Among the patients, 921 were HBeAg-positive (mean age, 32.5 years) and 446 were HBeAg-negative (mean age, 43 years). Approximately 75% of the patients were male.

At one year, significant advantages (P < .05) were reported in therapeutic responses (75% for telbivudine vs. 67% for lamivudine) in reducing HBV DNA (mean log10 6.5 vs. 5.5 copies) and in the percentage of patients with undetectable HBV DNA (60 vs. 40).

Dr. Lai’s report of two-year results showed a continuing benefit for telbivudine in both HBeAg-positive and HBeAg-negative patients (Tables 1 and 2). The results also revealed that the advantage of telbivudine in normalizing ALT levels gained statistical significance (P < .05) in HBeAg-positive patients between the first and second years of the trial.

Persistence of Benefits of Telbivudine over Lamivudine In Patients with Hepatitis B

Mr. Alexander is a freelance medical writer living in New York City.

Table 1  Efficacy of Telbivudine and Lamivudine at Year Two in HBeAg-Positive Patients

<table>
<thead>
<tr>
<th></th>
<th>Telbivudine</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>458</td>
<td>463</td>
</tr>
<tr>
<td>Therapeutic response (%)</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>HBV DNA levels reduced (mean log10)</td>
<td>–5.7</td>
<td>–4.4</td>
</tr>
<tr>
<td>HBV DNA levels undetectable by PCR (%)</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>Normalization of ALT (%)</td>
<td>70</td>
<td>62</td>
</tr>
</tbody>
</table>

All values: P < .05 versus lamivudine.

ALT = alanine transaminase; HBeAG = hepatitis B early antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.


Table 2  Efficacy of Telbivudine and Lamivudine at Year Two in HBeAg-Negative Patients

<table>
<thead>
<tr>
<th></th>
<th>Telbivudine</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>222</td>
<td>224</td>
</tr>
<tr>
<td>Therapeutic response (%)</td>
<td>78*</td>
<td>66</td>
</tr>
<tr>
<td>HBV DNA levels reduced (mean log10)</td>
<td>–5.0*</td>
<td>–4.2</td>
</tr>
<tr>
<td>HBV DNA levels undetectable by PCR (%)</td>
<td>82*</td>
<td>57</td>
</tr>
<tr>
<td>Normalization of ALT (%)</td>
<td>78</td>
<td>70</td>
</tr>
</tbody>
</table>

* All values: P < .05 versus lamivudine.

ALT = alanine transaminase; HBeAG = hepatitis B early antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.

Among patients recommended for treatment in accordance with guidelines of the AASLD and the Asia–Pacific Association for Study of the Liver (APASL) were those who were HBeAg-positive with ALT levels at two or more times the upper limit of normal (ULN). HBeAg loss or HBeAg seroconversion (undetectable serum HBV DNA) and virological response favored telbivudine. The rate of failed treatment was lower in the telbivudine group, as follows:

- HBeAg-positive patients: 6.8% with telbivudine, 18.8% with lamivudine (P < .001)
- HBeAg-negative patients: 0.9% with telbivudine, 7.6% with lamivudine (P < .001)

Two analyses found less resistance for telbivudine than for lamivudine in all pairwise comparisons (P < .001). Adverse events were similar between the two groups, but there were more ALT elevations in the lamivudine patients, especially after week 24.

Dr. Lai concluded that telbivudine brought about greater therapeutic response; higher reductions in HBV DNA; a higher number of patients becoming HBV DNA–negative (as shown on the polymerase chain reaction [PCR] assay) more quickly; and more responses in patients whose ALT values had been two or more times the ULN.

Di Bisceglie et al.

A further GLOBE trial analysis, reported by Adrian M. Di Bisceglie, MD, Chairman of Public Policy for AASLD and Professor of Internal Medicine at Saint Louis University School of Medicine, confirmed the clinical value of early HBV suppression in nucleoside-treated patients with chronic HBV infection. Dr. Di Bisceglie noted that prior results with lamivudine (Epivir-HBV) and adefovir dipivoxil (Hepsera, Gilead) had suggested that early viral suppression, at either six or 12 months, predicted the lowest rate of subsequent resistance. Similarly, early viral suppression was linked to improved therapeutic outcomes. Understanding the quantitative relationships between early viral suppression and subsequent responses could help in developing optimal patient management strategies, he said.

Investigators evaluated two-year outcomes separately in HBeAg-positive and HBeAg-negative patients in relation to four strata of HBV DNA levels achieved by week 24:

- undetectable levels according to PCR: below 300 copies/ml
- quantitation limit: to 10² copies/ml, to 10³ to 10⁴ copies/ml, or to more than 10⁴ copies/ml

Among patients achieving PCR-undetectable levels, the data analysis revealed a strong correlation between antiviral efficacy at week 24 and HBV DNA suppression at two years in both the telbivudine and lamivudine groups; however, there was generally greater suppression for all strata for telbivudine in both HBeAg-negative and HBeAg-positive patients. The difference was most pronounced in patients with more than four log reductions at 24 weeks (20% for telbivudine and 7% for lamivudine in HBeAg-positive patients and 20% for telbivudine and 5% for lamivudine in HBeAg-negative patients).

General Considerations

What should clinicians do for patients whose responses are weak or declining early in treatment?

In the past, Dr. Di Bisceglie explained, clinicians were reluctant to treat patients too early, partly to save therapy for those with more severe disease and in part because of the paucity of treatment options. He said that with the advent of more treatment approaches, “we are more willing to embark on longer-term treatment strategies.”

For initial therapy, either entecavir (Baraclude, Bristol-Myers Squibb) or telbivudine would be good choices; however, he added:

- The nice thing about telbivudine is that it has a very rapid antiviral effect—maybe one of the most rapid. So I would definitely think of it as first-line in someone who needs quick action, for example, someone in whom chemotherapy has stimulated a hepatitis B reactivation, or an elderly person with advanced disease where quick control is important.

We need to learn from the HIV community. They feel it is important to combine drugs to minimize resistance. That is the future—using two drugs that work with slightly different mechanisms to inhibit the emergence of resistance.

The paradigm for hepatitis B is shifting. So far we’ve studied agents for a year or two. But people need indefinite, long-term therapy. The longer we treat, the more resistance becomes an issue. When resistance occurs, having more agents to change and add is better for patients.

Actually, some combinations have already been studied. As for combining agents as an option among patients who have experienced loss of efficacy with a single agent, Dr. Di Bisceglie said that studies of lamivudine and adefovir have shown that although combining the agents does not appreciably add to either efficacy or toxicity, it does reduce the risk of viral resistance.