Histologic Assessment of Long-term Entecavir Treatment in Chronic Hepatitis B Patients

Yoshiaki Katoana, Hiromitsu Kumada, Haruhiko Kobashib, Joji Toyotac, Osamu Yokosukad, Koichi Takaguchie, Masayoshi Kagef, Mitsuhiro Miyarama, Furum Imazekig, Hiroshi Ishikawah, Taku Serusiig, Masao Omataj

Introduction

- In large clinical trials, elevated baseline HBV DNA has been demonstrated to be a significant risk factor for cirrhosis and hepatocellular carcinoma.
- HBV DNA suppression with antiviral therapy can significantly improve liver histology in HBeAg positive patients.
- Entecavir (ETV) demonstrated potent suppression of HBV DNA replication and improvement in liver histology in nucleoside-naive and lamivudine-refractory (LVDV) Japanese patients with chronic hepatitis B (CHB) (CRB) studies ETV-051 and ETV-052.
- All patients who completed studies ETV-053 and ETV-052 could enroll in this long-term study (ETV-053/052/060).

Methods

Study population

- The Long-term Histology Cohorts from Japan consist of patients who:
  - were initially treated with ETV in studies ETV-053 or ETV-052
  - subsequently enrolled on 052/060.
- had biopsies from three time points: baseline, Week 48 and Week 148.

ETV-053/052/060: eligibility

- Eligibility criteria (ETV-053 and ETV-052):
  - CHB infection with compensated liver disease
  - HBV DNA ≤ 200 copies/mL, by PCR assay
  - ETV-053:
    - ≥ 12 weeks prior treatment with anti-HBV nucleoside analogues
    - ≥ 20 weeks prior lamivudine therapy, ongoing at the time of randomization; or
    - documented evidence of infection with HBV-carrying LVDV substitutions
      - ALT 1-3x ULN
      - HBeAg (or HBeAb) absence.

ETV-052:
- Enrollment immediately after completion of ETV-053 or ETV-052 with no gap in dosing.
- Patients enrolling from ETV-053: 0.5 mg for a total of up to 148 weeks (3 years) of ETV treatment
- Patients enrolling from ETV-052: 1.0 mg for a total of up to 148 weeks (3 years) of ETV treatment

Efficacy and resistance analyses of the Long-term Histology Cohorts from Japan

- Efficacy assessments at Week 48 (1 year) and Week 148 (3 years) included proportion of patients with:
  - histologic improvement (2-point decrease in Knodell necroinflammatory score).
  - improvement in fibrosis (≥ 3-point decrease in Knodell fibrosis score)
  - detectable HBV DNA by PCR.
- ALT normalization (ALT < 2x ULN).
- Resistance:
  - Patented samples from all baseline and all patients with HBV DNA >400 copies/mL at Week 148 (or last treatment measurement for patients discontinuing prior to Week 148) were analyzed for substitutions associated with ETV resistance.
- All patients with virologic breakthrough (≥ 1 log increase from nadir on two consecutive measurements) were also genotyped.

Results

Table 1: Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ETV-053</th>
<th>ETV-052</th>
<th>ETV-053/052/060</th>
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<tbody>
<tr>
<td>Age, mean (years)</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Male, %</td>
<td>29 (70)</td>
<td>28 (76)</td>
<td>28 (76)</td>
</tr>
<tr>
<td>HBeAg, %</td>
<td>28 (76)</td>
<td>29 (70)</td>
<td>29 (70)</td>
</tr>
<tr>
<td>HBV DNA, log copies/mL</td>
<td>2.94 (1.05)</td>
<td>2.94 (1.05)</td>
<td>2.94 (1.05)</td>
</tr>
<tr>
<td>ALT, ULN, mean (SD)</td>
<td>155 (142)</td>
<td>155 (142)</td>
<td>155 (142)</td>
</tr>
<tr>
<td>Knodell HAI score, mean (SD)</td>
<td>9.0 (4.0)</td>
<td>9.0 (4.0)</td>
<td>9.0 (4.0)</td>
</tr>
<tr>
<td>Knodell fibrosis score, mean (SD)</td>
<td>2.5 (1.3)</td>
<td>2.5 (1.3)</td>
<td>2.5 (1.3)</td>
</tr>
<tr>
<td>HBV genotypes, C, %</td>
<td>37 (100)</td>
<td>37 (100)</td>
<td>37 (100)</td>
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</table>

Table 2: Histologic, Virologic and Biochemical Endpoints at Week 148

<table>
<thead>
<tr>
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<th>ETV-053</th>
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<th>ETV-053/052/060</th>
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<tbody>
<tr>
<td>Mean change from baseline in Knodell HAI score (SE)</td>
<td>-7.3 (0.48)</td>
<td>-7.3 (0.48)</td>
<td>-7.3 (0.48)</td>
</tr>
<tr>
<td>Mean change from baseline in Knodell fibrosis score (SE)</td>
<td>-8.0 (0.37)</td>
<td>-8.0 (0.37)</td>
<td>-8.0 (0.37)</td>
</tr>
<tr>
<td>Mean change from baseline in HBV DNA by PCR, log copies/mL (SE)</td>
<td>-4.0 (1.17)</td>
<td>-4.0 (1.17)</td>
<td>-4.0 (1.17)</td>
</tr>
<tr>
<td>ALT (n=12 ULN, e, %)</td>
<td>5.0 (86)</td>
<td>5.0 (86)</td>
<td>5.0 (86)</td>
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Table 3: Mean peak count and Altarea from Week 148

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<tr>
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<th>Week 48</th>
<th>Week 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean peak count, 10^5 PL (SE)</td>
<td>4.33 (0.36)</td>
<td>4.33 (0.36)</td>
</tr>
<tr>
<td>ALT/peak count (10^5 PL)</td>
<td>16.65 (6.03)</td>
<td>16.65 (6.03)</td>
</tr>
<tr>
<td>ALT/virologic breakthrough</td>
<td>16.14 (5.29)</td>
<td>16.14 (5.29)</td>
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Figure 1: Distribution of Knodell Necroinflammatory Scores at Baseline, Week 48 and Week 148

Figure 2: Histologic Improvement Through Week 148

Figure 3: Distribution of Knodell Fibrosis Scores at Baseline, Week 48 and Week 148

Figure 4: Improvement in Knodell Fibrosis Score through Week 148

Summary of Results

- These data on ETV treatment resulted in histologic improvement in 100% of nucleoside-naive and 89% of LVDV patients.
- Treatment with ETV beyond 48 weeks resulted in further improvement in fibrosis score and ALT values.
- High proportions of both naïve and LVDV patients achieved HBV DNA suppression and ALT normalization during 3 years of ETV.

Conclusions

- The results from these cohorts demonstrate that long-term continuous entecavir treatment results in durable suppression of HBV replication and significant histological improvement in nucleoside-naive and LVDV patients.

References


Disclosures

- The following people have conflict of interest: Yoshiaki Kato, Hirofumi Kumada, Haruhiko Kobashi, Joji Toyoda, Osamu Yokosuka, Koichi Takagiuchi, Masayoshi Kage, Mitsuhiro Miyawara, Furum Imazeki, Hiroshi Ishikawa, Taku Seru, Masao Omata.