Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers

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Background

- In the United States, approximately 30 percent of persons infected with the human immunodeficiency virus (HIV) are also coinfected with the hepatitis-C virus (HCV).

- Standard of care, prior to 2011, included pegylated interferon and ribavirin.

- The addition of NS3/4A protease inhibitors to pegylated interferon and ribavirin (triple therapy) has transformed HCV treatment.

- Studies have shown improved SVR (cure) rates with triple therapy.

- Interactions between the new HCV medications and HIV medications have not been fully evaluated.

Background

• Boceprevir (NS3/4A protease inhibitor) is partly metabolized by **CYP3A4/5** and is a strong **inhibitor** of **CYP3A4/5**.\(^2\)

• Etravirine is a substrate for **CYP3A**, 2C9, and/or 2C19. It is an inducer of **CYP3A** and an inhibitor of 2C9 and/or 2C19.\(^3\)

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Hypotheses

- Boceprevir concentrations will be decreased in the presence of etravirine.
  - Boceprevir $C_{\text{trough}}$ is **reduced** an average of 44% by efavirenz (CYP3A inducer).\textsuperscript{4}

- Etravirine concentrations will be increased in the presence of boceprevir.
  - Boceprevir **increases** midazolam (CYP3A substrate) AUC by 5.3-fold.\textsuperscript{4}

\textsuperscript{4} Kasserra CH et al. 18th Conference on Retroviruses and Opportunistic Infections. Boston, MA2011.
Objectives

• Primary objective: determine the bioequivalence of boceprevir and etravirine AUC, $C_{\text{max}}$, and $C_{\text{trough}}$ used alone and in combination in HIV/HCV seronegative healthy volunteers.

• Secondary objectives included: observed changes in other PK parameters and assessments of the safety and tolerability of the two drugs when used alone and in combination.
Methods

Enrolled Subjects (N=20):
- Healthy HIV-1/HCV seronegative men and non-pregnant women between 18 and 60 years of age were eligible.

Randomized Crossover Design to receive three sequences:
- Sequences included:
  - Boceprevir: 800 mg every 8 hours
  - Etravirine: 200 mg every 12 hours
  - Boceprevir + Etravirine: same dosing regimen

• 11-14 days of therapy
• ≥ 14 day “washout” between sequences

Pharmacokinetic Analysis:
- Intensive 8- or 12-hour PK analysis
- Standardized moderate fat breakfast (600-700kcal; 45% carbohydrates, 15% protein, 40% fat) before drug administration.
- Observed dosing.
Analytical and PK Methods

- **Bioanalyses**
  - Validated HPLC with MS/MS detection for boceprevir with LLQ=5ng/mL.
  - Validated HPLC/UV assay for etravirine with LLQ=20ng/mL

- **Pharmacokinetic Methods**
  - Etravirine and boceprevir pharmacokinetics determined with non-compartmental methods (WinNonLin v5.3)
Statistical Methods

- Geometric mean ratios (GMR) and 90% CI for the combination sequence vs. alone were evaluated using two one-sided $t$ tests.

- The hypothesis of equivalence ($\text{AUC}_{(0,\tau)}, \ C_{\text{max}}, C_8$ for boceprevir and $C_{\text{min}}$ for etravirine) was rejected if the lower confidence limit was $<0.8$ or the upper confidence limit was $>1.25$.

- Other PK parameters were compared using paired $t$-tests.
Results

- Twenty-six subjects enrolled with 20 subjects completing all three sequences.

- Of the 6 subjects not included in PK analyses: 4 due to rashes from etravirine, 1 due to CNS effects, and 1 due to a viral illness.

<table>
<thead>
<tr>
<th>Demographic Information</th>
<th>Completed Subjects, N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs): median, range</td>
<td>36 (18-59)</td>
</tr>
<tr>
<td>Weight (kg): median, range</td>
<td>73 (56-91)</td>
</tr>
<tr>
<td>Females, n(%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Caucasians, n(%)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>African Americans, n(%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Hispanics, n(%)</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>
Etravirine Results Differ From Hypothesis

<table>
<thead>
<tr>
<th></th>
<th>Mean (CV %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC(_{(0,T)}) (ng*h/mL)</td>
</tr>
<tr>
<td>ETV alone</td>
<td>7698 (33%)</td>
</tr>
<tr>
<td>ETV + BOC</td>
<td>5957 (54%)</td>
</tr>
<tr>
<td>GMR (ETV + BOC vs.</td>
<td>0.77</td>
</tr>
<tr>
<td>ETV alone)</td>
<td></td>
</tr>
<tr>
<td>Percent change</td>
<td>↓ 23%</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.66-0.91</td>
</tr>
</tbody>
</table>

- CL/F and V/F GMR were 1.29 (p=0.112) and 1.33 (p=0.0315), respectively.
- T1/2 not statistically different p=0.738
Boceprevir Results Differ From Hypothesis

<table>
<thead>
<tr>
<th></th>
<th>Mean (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC(_{(0,\tau)}) (ng*h/mL)</td>
</tr>
<tr>
<td>BOC</td>
<td>4601 (47%)</td>
</tr>
<tr>
<td>BOC + ETV</td>
<td>5047 (30%)</td>
</tr>
<tr>
<td>GMR (BOC + ETV vs. BOC)</td>
<td>1.10</td>
</tr>
<tr>
<td>Percent Change</td>
<td>↑ 10%</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.94-1.28</td>
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</tbody>
</table>

- CL/F and V/F GMR were 0.91 (p=0.3161) and 0.84 (p=0.3276)
- Difference in t1/2 was not statistically different as well p=0.6771
Safety and Tolerability

All clinical and laboratory adverse events observed in the study were graded as mild or moderate.

<table>
<thead>
<tr>
<th>Adverse Events Observed</th>
<th>Boceprevir Alone (n=21)</th>
<th>Etravirine Alone (n=22)</th>
<th>Combination (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Common, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered Taste</td>
<td>18 (86%)</td>
<td>-</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Frequency &gt;10%, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4 (19%)</td>
<td>5 (23%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (14%)</td>
<td>1 (5%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (19%)</td>
<td>-</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (19%)</td>
<td>-</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (9%)</td>
<td></td>
<td>4 (16%)</td>
</tr>
</tbody>
</table>
Possible Mechanism

- Possible mechanisms:
  - Reduction in bioavailability – reduced etravirine solubility and/or induction of efflux transporters (i.e. P-gp, MRP, BCRP)
  - Hepatic enzyme induction – Boceprevir induction of CYP3A, 2C9, and/or 2C19
  - Protein binding displacement – Displacement increasing clearance of etravirine
    - Etravirine is 99.9% protein bound.\(^3\)
    - Similar interaction observed between telaprevir and methadone.
    - Total concentrations of methadone’s AUC, \(C_{\text{max}}\), and \(C_{\text{min}}\) were reduced 29%, 29%, and 31%, respectively.\(^5\) Unbound methadone concentrations unchanged.

5. R. van Heeswijk AV et al. EASL The International Liver Congress 2011. Berlin, Germany 2011
Clinical Relevance

- Clinically relevant limit = 0.5, 2.0\(^6,7\)
- Study eliminated many confounding factors.
- Coadministration of etravirine with boceprevir decreased etravirine’s AUC 23%, \(C_{\text{max}}\) 24%, and \(C_{\text{min}}\) by 29%.

<table>
<thead>
<tr>
<th>Other Antiretroviral’s Effect on Etravirine(^8,9)</th>
<th>Percent change in ETV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/ritonavir 600/100 mg BID</td>
<td>↓ 37%</td>
</tr>
<tr>
<td>Tenofovir 300 mg QD</td>
<td>↓ 19%</td>
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</tbody>
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Conclusions

• Boceprevir concentrations were not altered to a clinically relevant level by etravirine.

• Etravirine concentrations could possibly reach clinical relevance in a clinical setting.

• Further research needed to evaluate multiple drug combination interactions in coinfected population, as well as research to elucidate the mechanism behind the interaction observed in this study.
Acknowledgements

- This study was supported by a research grant from the Investigator-Initiated Studies Program of Merck Sharpe & Dohme Corp. to J. Kiser.

- The CAVP lab for all of their great work.

- The study participants.

- The nurses and staff of the University of Colorado Hospital General Clinical Research Center.