Pharmacokinetic interaction between etravirine and lopinavir/ritonavir


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Abstract

Background
Etravirine (ETR; TMC125) is a next-generation NNRTI with demonstrated activity in treatment-experienced, HIV-1-infected patients. A previous interaction trial in HIV-negative volunteers demonstrated increased ETR exposure when co-administered with lopinavir/ritonavir (LPV/r) (soft-gel formulation). This study re-evaluated the pharmacokinetics of ETR and LPV/r when LPV/r was administered as the Meltrex® formulation.

Methods
Open-label, randomized, two-way, two-period crossover trial. ETR 200mg bid was given for 8 days. After 14 days washout, LPV/r 400/100mg bid was administered for 16 days; ETR 200mg bid was co-administered on Days 9–16. Steady-state pharmacokinetics were assessed over 12 hours for ETR, lopinavir (LPV) and ritonavir (RTV) alone and when co-administered. Pharmacokinetic (PK) parameters were obtained by non-compartmental analysis. Safety and tolerability were assessed.

Results
Sixteen volunteers participated (11 male/5 female). PK results are given below (Table 1).

Table 1. Mean (± SD) PK parameters for ETR and LPV alone and co-administered

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ETR Alone (N=16)</th>
<th>ETR With LPV/r (N=16)</th>
<th>LSM ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin</td>
<td>451 ± 121</td>
<td>253 ± 84</td>
<td>0.55 (0.49–0.62)</td>
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<tr>
<td>Cmax</td>
<td>905 ± 187</td>
<td>643 ± 163</td>
<td>0.70 (0.64–0.78)</td>
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<tr>
<td>AUC0–12h</td>
<td>8,036 ± 1,779</td>
<td>5,250 ± 1,416</td>
<td>0.65 (0.59–0.71)</td>
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<tr>
<td>LPV</td>
<td></td>
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<tr>
<td>Cmin</td>
<td>5.3 ± 1.9</td>
<td>4.3 ± 1.5</td>
<td>0.80 (0.73–0.88)</td>
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<tr>
<td>Cmax</td>
<td>11.2 ± 2.9</td>
<td>9.8 ± 1.9</td>
<td>0.89 (0.82–0.96)</td>
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<tr>
<td>AUC0–12h</td>
<td>96.8 ± 21.8</td>
<td>84.5 ± 17.7</td>
<td>0.87 (0.83–0.92)</td>
</tr>
</tbody>
</table>

SD = standard deviation; LSM = least square means; CI = confidence interval; Cmin = minimum plasma concentration; Cmax = maximum plasma concentration; AUC0–12h = area under the plasma concentration-time curve from time of administration to 12 hours after dosing.

RTV pharmacokinetics were unchanged. The most frequent adverse event (AE) was headache in six volunteers (grade 1). One grade 3 increase of triglycerides was reported during co-administration.

Conclusions
In contrast to the results of the study performed with the soft-gel LPV/r co-administration of ETR with LPV/r (Meltrex®) resulted in a 30–45% decrease in ETR pharmacokinetics. The decrease of LPV PK parameters by 13–20% when combined with ETR is similar to earlier reported data and is not considered clinically relevant. Given that the effect of LPV/r on ETR pharmacokinetics is comparable to that seen with darunavir/ritonavir (DRV/r) in previous trials, which demonstrated favorable ETR efficacy and safety, ETR and LPV/r can be co-administered without dose adjustments.

Efficacy of ETR co-administered with DRV/r at Week 96

References