Dolutegravir Pharmacokinetics in HIV-Infected Pregnant and Postpartum Women

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Introduction

Antiretroviral therapy (ART) can reduce the risk of perinatal transmission to < 1% and is recommended for all pregnant women. Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) recommended for INSTI-naïve and some INSTI-experienced patients with human immunodeficiency virus type 1 (HIV-1).

Methods

The IMPAACT P1026s study (ClinicalTrials.gov identifier NCT00422889) is an ongoing non-randomized, open-label, parallel-group, multi-center phase-IV prospective study of antiretroviral pharmacokinetics and safety in HIV-infected pregnant women that includes an arm for dolutegravir. Samples were collected at 20-28 weeks gestation, 30-38 weeks gestation and between 3 to 12 weeks following delivery. Serial blood collection was drawn at pre-dose, 1, 2, 4, 6, 8, 12 and 24 hours post-dose.

Results

Maternal Pharmacokinetics

• Data were available for 2nd trimester (n = 9), 3rd trimester (n = 15), postpartum (n = 9) and infant washout (n = 10). [Table 1]
• DTG AUC was 25 – 30% lower in the 2nd trimester compared to paired postpartum data; differences were not significant (n=4) and 7 for 2nd and 3rd trimester comparisons to postpartum). [Table 2, Figure 1]
• DTG Cmax was significantly lower in the 3rd trimester compared to paired postpartum data. Cmax were 41% lower in both 2nd and 3rd trimester, but differences were not significant. [Table 2, Figure 2]
• 6/7 (86%) subjects in the 2nd trimester, 12/15 (80%) subjects in the 3rd trimester and 8/9 (89%) subjects postpartum had an AUC above the 10th percentile (37.5 mcg/hr/mL) of non-pregnant adults.

Discussion and Conclusion

• AUC and trough DTG exposure appear to be lower in pregnancy compared to postpartum, but antepartum AUC and trough values are still similar to those seen in non-pregnant adults.
• During pregnancy, UGT1A1 activity is induced by increased progesterone levels.

Pharmacokinetic and pharmacodynamic data from all 10 infants: elimination half-life was 35 hours. [Table 3, Figure 3]

Table 2. Maternal Dolutegravir Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)</th>
<th>2nd Trimester</th>
<th>n = 9</th>
<th>3rd Trimester</th>
<th>n = 15</th>
<th>Postpartum</th>
<th>n = 9</th>
<th>Historical Control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (mcg*hr/mL)</td>
<td>58.4 (47.6 - 64.5)</td>
<td>48.7 (40.3 - 57.6)</td>
<td>71.1 (60.8 - 83.1)</td>
<td>53.6 (27)</td>
<td></td>
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</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>0.86 (0.64 - 1.98)</td>
<td>1.01 (0.75 - 1.42)</td>
<td>1.76 (0.69 - 2.29)</td>
<td>-</td>
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<tr>
<td>Cmin (mcg/mL)</td>
<td>4.59 (3.89 - 5.22)</td>
<td>3.92 (3.36 - 4.44)</td>
<td>5.10 (3.73 - 7.23)</td>
<td>3.67 (20)</td>
<td></td>
<td></td>
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<tr>
<td>T1/2 (hr)</td>
<td>0.88 (0.69 - 1.37)</td>
<td>0.91 (0.74 - 1.21)</td>
<td>1.70 (0.76 - 2.00)</td>
<td>1.11 (46)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>0.86 (0.78 - 1.05)</td>
<td>1.03 (0.87 - 1.24)</td>
<td>0.70 (0.60 - 0.86)</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>10.5 (8.7 - 12.6)</td>
<td>11.2 (13.6 - 13.9)</td>
<td>12.3 (10.5 - 15.6)</td>
<td>14</td>
<td></td>
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</tr>
</tbody>
</table>

¹Historical data from Trivago® (dolutegravir) package insert, represented as geometric mean (GM)

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References