Increased dolutedgravir exposure in HIV patients switched from ritonavir to cobicistat

Cristina Gervasoni1, Agostino Riva1, Amedeo Capetti2, Valeria Cozzi2, Giuliano Rizzardini2, Emilio Clementi2, Massimo Galli2, Dario Cattaneo2

1Department of Infectious Diseases and 2Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy

Background
- Cobicistat is an inhibitor of cytochrome P4503A (CYP3A) enzymes that has been marketed in some countries as pharmacokinetic enhancer
- Cobicistat has a lower potential for drug interactions than ritonavir, due to its more selective inhibition of CYP3A and lower likelihood for enzymatic induction
- Studies in healthy volunteers have shown that the bioavailability of darunavir/cobicistat 800/150 mg is similar to that of darunavir/ritonavir 800/100 mg coadministered as single agents
- No studies have previously investigated the effect of cobicistat versus ritonavir on dolutegravir exposure; however, given the limited contribution of CYP3A isozymes on dolutegravir metabolism, a direct role of cobicistat on increased dolutegravir bioavailability is unlikely

Aims of the study
- To carry out a pharmacokinetic survey in HIV-infected patients switching from darunavir/ritonavir (800/100 mg/daily) to darunavir/cobicistat (800/150 mg/daily) and given dolutegravir (50 mg/daily) as part of their antiretroviral therapy

Methods
- A consecutive series of HIV-infected patients undergoing therapeutic drug monitoring (TDM) of dolutegravir and darunavir plasma trough concentrations before (TDM 1) and after (TDM 2) the switch from ritonavir to cobicistat were considered
- Collected blood samples were taken 24 hours after the last drug intake (a time window of 20 min was considered acceptable), immediately before drug administration
- Drug concentrations were assessed by high performance liquid chromatography method with UV detection. The lower limit of quantifications (LOQ) were:
  - darunavir 150 ng/mL
  - dolutegravir 50 ng/mL
- Comparisons were performed by paired t-tests

Results 1: patients characteristics

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>TDM 1</th>
<th>TDM 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 6</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>Caucasians (%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Time from the first TDM (days)</td>
<td>79 ± 62</td>
<td>79 ± 62</td>
</tr>
<tr>
<td>CD4 cell count (cells/mL)</td>
<td>650 ± 399</td>
<td>559 ± 376</td>
</tr>
<tr>
<td>Patients with viral load &gt;37 copies/mL (n)</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>Serum alanine aminotransferase (IU/mL)</td>
<td>39 ± 16</td>
<td>37 ± 15</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.14 ± 0.33</td>
<td>1.22 ± 0.29</td>
</tr>
<tr>
<td>Darunavir trough concentrations (ng/mL)</td>
<td>2033 ± 976</td>
<td>1979 ± 940</td>
</tr>
<tr>
<td>Dolutegravir trough concentrations (ng/mL)</td>
<td>599 ± 317</td>
<td>1149 ± 605*</td>
</tr>
</tbody>
</table>

*Data were given as mean ± standard deviation; **p<0.001

Results 2: Drug concentrations

Interpretations of the results
- Ritonavir could potentially decrease dolutegravir concentrations by induction of glucuronidation. Accordingly, the switch to cobicistat, by removing the ritonavir-mediated induction of dolutegravir metabolism, is expected to increase dolutegravir exposure
- Cobicistat could potentially exert a higher degree of inhibition of intestinal efflux transporters than ritonavir. Accordingly, the switch from ritonavir to cobicistat might results in increased dolutegravir intestinal absorption and systemic bioavailability

Conclusions
- We confirmed in a real-life setting that the switch from ritonavir to cobicistat resulted in a comparable boosting effect on darunavir exposure
- Cobicistat significantly increased dolutegravir concentrations. In clinical practice, this effect might become relevant in poorly-compliant patients or when the dose of dolutegravir should be doubled (in patients with resistance to integrase inhibitors or treated with drugs known to reduce dolutegravir disposition)
- Co-administration of dolutegravir and cobicistat has not shown effect on serum creatinine concentrations, suggesting that this combination does not result in addictive renal toxicity at least in the short-term
- In view of these results, ritonavir and cobicistat not only differ in terms of selectivity for cytochrome inhibition but also for patterns of modulation of phase II metabolic enzymes and drug transporters. These differences may have potential clinical implications when HIV-infected patients are switched from one to another booster, dependently on which medications are co-administered

Abstract: 410