O315. The pharmacokinetic and safety profile of raltegravir and ribavirin, when dosed separately and together, in healthy volunteers

J Ashby1*, LJ Garvey2, OW Erlwein3, H Lamba1, R Weston1, K Legg3, MO McClure3, L Dickinson4, A D’Avolio5, DJ Back4, A Winston3

From Tenth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 7-11 November 2010

Purpose of the study
Treatment of chronic hepatitis C virus (HCV) infection in HIV-1 co-infected individuals remains challenging due to numerous factors including drug-drug interactions. The aim of this study was to assess the safety and pharmacokinetic (PK) profile of raltegravir, a recently licensed antiretroviral agent, and ribavirin, when dosed separately and together.

Methods
Fourteen healthy volunteers (mean (standard deviation) age 35 (10) years, 71% male) entered this phase I PK study and received single dose ribavirin (800 mg) on day 1 (phase 1). Following a wash-out period, subjects received raltegravir (400 mg twice daily) on days 15-19 (phase 2) and single dose ribavirin (800 mg) with raltegravir (400 mg) on day 20 (phase 3). Intensive PK sampling was undertaken on days 1, 19 and 20 and differences in geometric mean ratios (GMR) for PK parameters between study periods assessed.

Results
No statistically significant differences in PK parameters were observed for raltegravir between phases 2 versus 3. A statistically significant decrease in maximum plasma concentration (Cmax) and increase in time to maximum plasma concentration (Tmax) was observed for ribavirin in phase 3 compared to phase 1 (GMR (95% CI) 0.79 (0.62 - 1.00) and 1.39 (1.08 - 1.78), respectively; Table 1) whereas no significant differences in other ribavirin PK parameters were observed between study phases including area under-time-curve (AUC) or minimum observed plasma concentration (Cmin). No clinically significant safety concerns were reported.

Conclusions
The PK profile of ribavirin is altered when administered with raltegravir (reduced Cmax and increased Tmax). This is unlikely to be of clinical significance or have an impact on the antiviral effects of ribavirin in HIV-1 and HCV co-infected subjects.

Table 1

<table>
<thead>
<tr>
<th>Ribavirin PK parameters</th>
<th>phase I (ribavirin alone)</th>
<th>phase 3 (ribavirin with raltegravir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ½, h</td>
<td>6.04 (5.29 - 6.90)</td>
<td>6.77 (5.56 - 8.25)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>1.61 (1.12 - 2.11)</td>
<td>2.23 (1.65 - 3.01)</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>630.09 (490.91 - 808.54)</td>
<td>496.71 (407.38 - 605.76)</td>
</tr>
<tr>
<td>Cmin, ng/mL</td>
<td>184.71 (148.59 - 229.61)</td>
<td>186.98 (157.83 - 221.56)</td>
</tr>
<tr>
<td>AUC0-12</td>
<td>3325.83 (2703.34 - 4091.66)</td>
<td>2941.03 (2323.27 - 3722.20)</td>
</tr>
</tbody>
</table>

© 2010 Ashby et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Author details
1 Imperial College Healthcare NHS Trust, GU/HIV Medicine, London, UK.
2 Imperial College London, Section of Infectious Diseases, HIV Medicine, London, UK. 3 Imperial College London, Section of Infectious Diseases, London, UK.
4 University of Liverpool, Department of Pharmacology and Therapeutics, Liverpool, UK.
5 University of Turin, Pharmacokinetics and Pharmacogenetics Laboratory, Torino, Italy.

Published: 8 November 2010

doi:10.1186/1758-2652-13-S4-O33

Submit your next manuscript to BioMed Central and take full advantage of:
• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit