Journal of the International AIDS Society

Poster presentation

Open Access

Plasma concentrations of boosted and unboosted atazanavir are predicted by 63396C>T SNP in the PXR gene

M Siccardi*[1], A D'Avolio[1], L Baietto[1], A Calcagno[1], SE Gibbons[2], M Sciandra[1], S Bonora[1], SH Khoo[2], DJ Back[2], G Di Perri[1] and A Owen[2]

Address: [1]Department of Infectious Diseases, University of Torino, Torino, Italy and [2]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

* Corresponding author

from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, **11**(Suppl 1):P233 doi:10.1186/1758-2652-11-S1-P233

This abstract is available from: http://www.jiasociety.org/content/11/S1/P233

Purpose of the study

Atazanavir (ATV) is administered at the usual adult dose of 300 mg with 100 mg of ritonavir (RTV) once a day (boosted). However, 400 mg once a day (unboosted) is also used in some settings. ATV plasma concentrations are influenced by efflux transporters, influx transporters and metabolism enzymes. The expression of many of these proteins is regulated by nuclear receptors such as PXR. Recently polymorphisms in the regulatory region of the PXR gene have been reported to influence its expression and the activity of downstream genes, such as CYP3A4 and ABCB1. The aim of this study was to investigate whether polymorphisms in PXR influence trough concentrations (Ctrough) of boosted or unboosted ATV.

Methods

Patients were recruited in Torino, Italy, or from the Liverpool TDM registry, UK. Ethics committee approval was obtained for genotyping. Respective totals of 110 patients receiving unboosted ATV and 265 patients receiving boosted ATV as part of their antiretroviral therapy were included in this study. ATV plasma concentrations were quantified using validated LC-MS or HPLC-UV methods. Genotyping was conducted by real time PCR based allelic discrimination using standard methodology. Statistical analysis was conducted by Mann-Whitney or Spearman Rank to assess the effects of weight, age, gender, tenofovir (TDF) administration and genotype on ATV Ctrough.

Summary of results

No associations between patient demographics or TDF co-administration were observed with either unboosted or boosted ATV Ctrough. However, unboosted Ctrough was lower for individuals characterised by PXR 63396 T homozygosity compared to the other two groups (CC and CT), 66 (IQR, 36–90) ng/mL vs. 161 (IQR, 55–266) ng/mL ($p = 0.0001$). Similarly, boosted Ctrough concentrations were lower in patients with PXR 63396 T homozygosity compared to the other two groups (CC and CT), 458 (IQR, 283–838) ng/mL vs. 679 (IQR, 383–1051) ng/mL ($p = 0.02$).

Conclusion

Homozygosity for PXR 63396 T was strongly correlated with ATV Ctrough, which suggests that PXR is important in the regulation of disposition of this drug. The impact of 63396 C>T was more marked for unboosted ATV, presumably due to inhibition of CYP3A4 and ABCB1 by RTV in the boosted regimen. Further studies are now required to confirm this association, prior to prospective studies to define its clinical value for individualisation of ATV therapy.