Poster

[P27-3] P27-3: Anti-infective drugs (8): Antiviral

Chair: Birgit C. P. Koch, The Netherlands
Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall)

[P27-3-5] Interaction between darunavir and etravirine is partly mediated by CYP3A5 polymorphism

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Keywords: darunavir, etravirine, CYP3A5, polymorphism

Background

To assess the impact of the loss-of-function *CYP3A5*3* allele (rs776746, 6986A>G SNP) on darunavir (DRV) plasma concentrations

Methods

135 HIV-1 infected patients treated with DRV-based therapy were included in the study and plasma samples were obtained immediately before drug intake in order to determine DRV trough concentrations using an ultra performance liquid chromatography method (UPLC) with diode-array detection (DAD). Noteworthy is the fact that in 16 (11.9%) patients, etravirine (ETR) was combined with DRV. *CYP3A5* genotypes were determined using real time PCR method (TaqMan® genotyping assay). The patients were then classified into CYP3A5 expressors (*CYP3A5*1* allele carriers) and non-expressors (*CYP3A5*3* homozygous). Subsequently, the association between DRV plasma trough concentration ($[DRV]_{plasma}$) and CYP3A5 genotype-based expression status was analyzed.

Results

45% of the patients were classified as CYP3A5 expressors. In the whole cohort, mean $[DRV]_{plasma}$ was not different between CYP3A5 expressors and non-expressors (1894ng/ml [CI95%: 1566-2290] versus 1737ng/ml [CI95%: 1468-2057], p=0.43). However, in the subgroup of the 16 patients receiving DRV combined with ETR, a significantly lower $[DRV]_{plasma}$ was observed for CYP3A5 expressors when compared to non-expressors (1385ng/ml [CI95%:886.3-2165] versus 3141ng/ml [CI95%:2042-4831], p=0.007).

Conclusions

Interaction between DRV and ETR is partly mediated by *CYP3A5* polymorphism with lower DRV plasma trough concentrations in CYP3A5 expressors suggesting a specific ETR-driven CYP3A5 activation only in CYP3A5 expressors. Consequently, these patients might be more at risk of infra-therapeutic $[DRV]_{plasma}$. This potentially important observation is a good illustration of a genotype-based drug interaction, which could also have considerable consequences if translated to other CYP3A5-metabolized drugs. Further investigations are thus needed to confirm this association and to explore its clinical impact, mainly in the African population among whom CYP3A5 expressors are more frequent, before recommending systematic CYP3A5 pre-emptive genotyping for DRV-ETR co-administration.

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