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Lersivirine: a new NNRTI active across HIV-1 subtypes with a unique resistance profile

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Purpose of the study

Lersivirine (UK-453,051), a new potent NNRTI, displays novel binding with a unique *in vitro* resistance profile, and shows potential for use against transmitted NNRTI resistant virus and as a candidate for sequential NNRTI therapy. Further *in vitro* analyses have been performed to establish the breadth of activity and identify potential populations that might benefit from lersivirine therapy. Lersivirine activity against various HIV-1 subtypes and viruses with decreased susceptibility to etravirine (ETR) were characterised.

Methods

The PhenoSense™ assay was used to assess the antiviral activity of lersivirine against different HIV-1 subtypes (A, A1, B, BF, C, C/H, D, F, F1, G and H), and the circulating recombinant forms (CRFs) CRF01_AE and CRF02_AG. All were obtained from treatment-naïve patients. Nineteen additional clinical viruses with NNRTI resistance associated mutations (RAMs) were selected based on their reduced susceptibility to ETR.

Summary of results

Lersivirine was active against a panel of 80 clinically-derived viruses representing subtypes A to H, including several CRFs, from a range of geographical origins (geometric mean IC_{50} fold change [FC] to reference virus was 0.92). IC_{50} FC were < 2 for all viruses with the exception of 1 subtype BF and 1 subtype C (geometric mean IC_{50} FC: subtype BF = 0.98, 95% CI 0.64 - 1.49, n=7; subtype C = 1.07, 95% CI 0.88 - 1.30, n=25). Lersivirine retained activity (< 10 FC IC_{50}) for 11 of the 19 viruses with ETR resistance (> 2.9 FC IC_{50}, lower clinical cut-off). Overall, a direct correlation between lersivirine and ETR susceptibility was not found (R^2 = 0.002). This is consistent with different genotypic resistance profiles. Indeed to date, reduced susceptibility to lersivirine and ETR is associated with the presence of different specific NNRTI RAMs.

Conclusions

Lersivirine showed comparable activity across a range of viruses representing subtypes A to H. The activity of lersivirine against ETR- resistant viruses reflects significant differences in the resistance profiles of lersivirine and ETR consistent with the unique binding of lersivirine in the NNRTI binding pocket. Lersivirine has a distinctive *in vitro* resistance profile and may provide an additional therapy choice for patients with evidence of NNRTI resistance.

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