Nucleoside-associated mutations cause hypersusceptibility to etravirine (ETR)

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Abstract

Background
Nucleoside associated mutations (NAMs) have been implicated in hypersusceptibility (HS) to first-generation NNRTIs; HS has been associated with better clinical responses to NNRTIs. In-vitro HS to etravirine (ETR; TMC125) was investigated.

Methods
A panel of 29 HIV-1 recombinant clinical isolates with well-characterised HS to nevirapine (NVP) and efavirenz (EVR) was tested for ETR phenotypic susceptibility (PhenoSense™, Monogram Biosciences). The panel consisted of four groups: a) isolates with no mutations in reverse transcriptase (RT) (n=8); b) isolates with M184V alone (n=6); c) isolates with NAMs + M184V (n=8); d) isolates with NAMs (n=7). NAMs included amino acid changes at positions: 41, 65, 67, 69, 70, 115, 118, 151, 210, 215, and/or 219. In addition, isolates carrying the K103N mutation (n=11), with or without NAMs and other NNRTI mutations, as well as 1,027 wild-type routine clinical samples with no known NNRTI, NNRTI- or protease inhibitor (PI)-resistance mutations were tested. HS was defined as a fold-change in 50% effective concentration (FC) ≤0.4.

Results
The proportion of samples with HS to ETR, EFV and NVP, respectively, in each group was: a) 0%, 62.5% and 100%; b) 100%, 100% and 100%; c) 75%, 100% and 87.5%; d) 100%, 71% and 85.7%. Median FC values to ETR, EFV and NVP, respectively, in each group were: a) 0.53, 0.4 and 0.3; b) 0.27, 0.25 and 0.25; c) 0.29, 0.27 and 0.26; d) 0.26, 0.33 and 0.34. In addition, one sample with K103N and NAMs showed HS to ETR (FC=0.24). However, none of 10 samples with K103N alone (n=4) or with K103N + other NNRTI mutations, but no NAMs (n=6) showed HS to ETR. The median FC among samples with K103N was 1.18 (range 0.49–2.22) for ETR in contrast to 49 for EFV and >100 for NVP. Among wild-type samples, 2.8%, 3.1% and 9.0% showed HS to ETR, EFV, and NVP respectively.

Conclusions
Among the HIV-1 isolates studied, HS to ETR was mainly observed among those carrying NAMs or M184V. K103N-containing isolates did not exhibit HS to ETR; nevertheless, FC values were below the PhenoSense™ clinical cut-off for ETR (2.9). The potential impact of HS on response to ETR deserves further investigation. Please note that these data have been updated following the submission of this abstract.

References