An update of the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET-1 and DUET-2 clinical trial data

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Abstract

Background

Etravirine (ETR; TMC125) is a next-generation NNRTI with activity against NNRTI-resistant HIV-1 and a high genetic barrier to the development of resistance. Analyses of the pooled DUET-1 and DUET-2 Phase III clinical trials identified 13 ETR resistance-associated mutations (RAMs) (V90I, A98G, L100I, K101E/H/P, V106I, V179D/F, Y181C/V, and G190A/S). The presence of three or more of these RAMs was associated with decreased virologic response to ETR. In this study, additional statistical approaches were used to refine this list and improve the genotypic/phenotype correlation.

Methods

Effect of baseline resistance on virologic response (<50 copies/mL) to ETR at Week 24 was studied in patients not using enfuvirtide (ENF) de novo and excluding those who discontinued for other reasons than virologic failure (n=406). Multivariate analyses included logistic regression controlling for baseline viral load, darunavir (DRV) fold change in 50% effective concentration (FC) and NRTI sensitivity. Mutations were identified based on the association with decreased virologic response and/or increased ETR FC. Mutations in the reverse transcriptase (RT, amino- acids 1–400) were included in the final analysis if present in ≥5 patients.

Results

The analyses confirmed the impact on the response of the 13 ETR RAMs identified previously and also identified K101H, E138A and V179F at associated with a decreased virologic response and/or increased ETR FC. The V179F/T, Y181V, and G190S mutations were associated with the lowest virologic response, but were present in ≤5% of patients at baseline. Virologic response decreased in subgroups with increasing numbers of baseline ETR RAMs (7%, 61%, 56%, 38% for 0, 1, 2, ≥3 RAMs, respectively). Relative weighting of the 16 ETR RAMs improved the correlation between baseline ETR FC and the number of ETR RAMs.

Conclusions

A comprehensive analysis of baseline resistance data from DUET-1 and DUET-2 identified four additional mutations resulting in a list of 17 ETR RAMs: V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/F/T, Y181C/V, G190A/S, and M230L. The updated list of ETR RAMs and the relative weighting improved the relationship between genotypic and phenotypic susceptibility interpretations. Among the 17 ETR RAMs, Y181I and Y181V had the highest resistance, followed by L100I, K101P, Y181C, and M230L. Among the 17 ETR RAMs, mutations with the highest weight had a low prevalence. The virologic response was a function of the number and weight of the baseline ETR RAMs. A weighted mutation score of 0–2, 2.5–3.5, and 4 corresponded to response rates of 74% (highest response), 52% (intermediate response) and 38% (reduced response), respectively. This new genotypic interpretation system provides better guidance in the interpretation of ETR susceptibility.

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