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DETERMINATION OF PHENOTYPIC CLINICAL CUT-OFFS FOR ETRAVIRINE: POOLED WEEK 24 RESULTS OF THE DUET-1 AND DUET-2 TRIALS

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BACKGROUND: DUET-1 and DUET-2 are ongoing, randomized, placebo-controlled, double-blind, Phase III trials, demonstrating superior antiretroviral activity at 24 weeks of the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (ETR; TMC125) + background regimen (BR; darunavir/ritonavir + nucleoside reverse transcriptase inhibitors [NRTIs] ± enfuvirtide) versus placebo + BR in treatment-experienced patients. Phenotypic clinical cut-offs (CCOs) for ETR are presented.

METHODS: In pooled DUET, 599 patients received ETR. Phenotypic CCOs for Antivirogram were determined using ANCOVA models and data-mining techniques in patients not using for the first-time (de novo) enfuvirtide and excluding those who discontinued before 24 weeks for reasons other than virological failure ($n=403$).

RESULTS: Baseline ETR fold change (FC) in EC_{50} was a significant predictor of response (HIV-1 RNA <50 copies/ml) at 24 weeks. Baseline FC and responses to ETR were characterized by a continuum rather than a bimodal distribution. Inverse prediction of the ANCOVA model, with covariates baseline viral load, baseline CD4+ T-cell count and baseline darunavir FC, NRTI sensitivity and ETR FC, resulted in an initial CCO of 13, based on a 1 log greater response at week 24 versus placebo. As response in patients with baseline FC>13 was still substantial (37%), this value was considered an intermediate CCO. A FC value above which ETR provided no or little additional efficacy benefit (high CCO) could not reliably be established. Data-mining techniques allowed determination of a lower CCO of 3, below which patients exhibited the highest response rate. At baseline, 67%, 18% and 15% of patients had ETR FC=3, 3–13 and >13, respectively. At week 24, 71%, 50% and 37% of patients with FC=3, 3–13 and >13, respectively, reached <50 copies/ml.

CONCLUSIONS: Response in the ETR arms of the DUET trials decreased with increasing baseline ETR FC. The highest response rate was observed in the group of patients with ETR FC=3 (lower CCO).

The robust responses observed in a substantial number of patients with baseline ETR FC>13 (intermediate CCO) and the low number of observations in this subgroup did not allow for the determination of a high CCO. These CCOs provide phenotypic guidance for use of ETR in treatment-experienced HIV-1-infected patients.

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