121

Determination of phenotypic clinical cut-offs for etravirine (ETR): pooled Week 24 results of the DUET-1 and DUET-2 trials

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Abstract

Background

DUET-1 and DUET-2 are ongoing, randomised, placebo-controlled, double-blind, Phase III trials, demonstrating superior antiretroviral activity at 24 weeks of the NNRTI etravirine (ETR; TMC125) + background regimen (BR; darunavir with low-dose ritonavir [DRV/r] + NRTIs \pm enfuvirtide [ENF]) 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 analysis of covariance (ANCOVA) models and data-mining techniques in patients not using for the firsttime (*de novo*) ENF and excluding those who discontinued before 24 weeks for reasons other than virologic failure (n=403).

Results

Baseline ETR fold-change in 50% effective concentration (FC) was a significant predictor of response (HIV-1 RNA <50 copies/mL) at 24 weeks. Baseline FC and responses to ETR were characterised by a continuum rather than a bimodal distribution. Inverse prediction of the ANCOVA model, with covariates baseline viral load (VL), baseline CD4 cell count and baseline DRV 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. Since response in patients with baseline FC >13 was still substantial (37%), this value was considered an intermediate CCO. An 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 \leq 3, 3–13, and >13, respectively. At Week 24, 71%, 50% and 37% of patients with FC \leq 3, 3–13, and >13, respectively, reached VL <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 \leq 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.

Please note some of the data in the abstract have been updated in the poster



RAM = resistance-associated mutation ¹Madruga JV, et al. Lancet 2007;370:29–38; ²Lazarin A, et al. Lancet 2007;370:39–48





Response according to phenotypic ETR CCOs: pooled Week 24 DUET – patients not using ENF de novo

ETR CCO	Proportion of patients with VL <50 copies/mL (TLOVR), % (n)	Mean (SE) decrease in from baseline (NC:
_3	71 (190/269)	-2.67 (1.03)
3–13	50 (37/74)	-2.39 (1.21)
>13	37 (22/60)	-1.79 (1.42)
Overall placebo	36 (149/414)	-1.51 (1.42)
		Non-virologic failure exclu

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ETR FC vs ETR weighted mutation score – pooled DUET



Conclusions

- Based on the analysis of the Week 24 DUET virologic response data, CCOs were determined for ETR
- First time that phenotypic CCOs could be determined for an NNRTI
- A lower CCO of 3 and an intermediate CCO of 13 were identified for ETR
- the 'highest' response rate (71% VL <50 copies/mL) was observed in patients with baseline ETR FC ≤3
- an 'intermediate' response rate (50% VL <50 copies/mL) was observed in patients with baseline ETR FC between 3 and 13
- an upper CCO above which patients would no longer benefit from ETR could not yet be determined in this dataset, due to the small number of patients with FC >13 and the substantial virologic response rate in this subset of patients (37% VL <50 copies/mL)
- The majority of patients in DUET had an ETR baseline FC \leq 3: 66% (779/1190)

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