Poster No. 32

Impact of baseline NNRTI mutations on the virological response to TMC125 in the Phase III clinical trials DUET-1 and DUET-2

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Abstract

Background

TMC125 (etravirine, ETR) is a next-generation NNRTI, with activity against NNRTI-resistant HIV-1 and a high genetic barrier to the development of resistance. This analysis was aimed at identifying baseline genotypic determinants of decreased virological response to TMC125 (200mg bid) in the Phase III, double-blind, placebo-controlled trials, DUET-1 and DUET-2.

Methods

Effect of baseline phenotype (Antivirogram®) and genotype (virco®TYPE HIV-1) on the virological response to TMC125 at Week 24 was studied in the subgroup of patients not using enfuvirtide as a new drug in analyses and excluded patients who discontinued for other reasons than virological failure (n=406). Decreased virologic response was defined as a lower response than in the subgroup of patients with no detectable NNRTI resistance-associated mutations (RAMs) at baseline, (primary efficacy endpoint: <50 HIV-1 RNA copies/mL). Forty-four reverse transcriptase (RT) mutations were studied, but only those present in ≥5 patients at baseline were included in the final analyses.

Results

Of the 44 mutations studied, 26 were present in ≥5 patients at baseline. Univariate analyses identified the following mutations to be associated with decreased virological response to TMC125: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S (TMC125-RAMs). Isolates with A98G, K101E, Y181C, V179F, or G190A harboured more NNRTI mutations than isolates without these mutations. V179F was never present without Y181C. Y181V, G190S and V179F, which had the most pronounced effect on response, were present in <5% of patients. TMC125 fold change (FC) in EC_{50} increased with increasing numbers of NNRTI RAMs or TMC125 RAMs and was a strong predictor of virological response. Accordingly, virological response decreased progressively among subgroups with increasing numbers of TMC125 RAMs. The largest impact was observed in the subgroup of patients with >3 TMC125 RAMs at baseline.

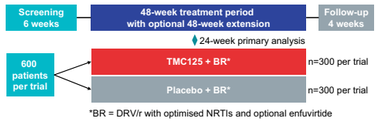
Conclusions

Thirteen mutations, mainly occurring in the presence of other NNRTI RAMs were associated with a decreased response to TMC125. The decrease was a function of the number of baseline TMC125 RAMs, with the largest impact in the subgroup of patients with >3 of those. Additional analyses will provide more insight into the role of these mutations, individually and combined, in resistance to TMC125.

Objectives

- The analyses aimed to
  - identify the baseline genotypic determinants of decreased virological response to TMC125, in the Phase III DUET-1 and DUET-2 trials (pooled data)
  - provide guidance in the interpretation of genotypic resistance information related to TMC125

DUET trials: design and inclusion criteria



*BR = DRV/r with optimised NRTIs and optional enfuvirtide

- Plasma viral load at screening: >5,000 HIV-1 RNA copies/mL
- Stable antiretroviral therapy for at least 8 weeks at screening, and remain on that treatment until baseline
- At least three primary protease inhibitor mutations at screening
- At least one NNRTI resistance-associated mutation (either at screening or in documented historical genotype)

BR = background regimen; DRV/r = darunavir with low-dose ritonavir

Methods

- Effect of baseline genotype on the virological response to TMC125, at Week 24, was studied in the subgroup of patients not using enfuvirtide as a new drug (i.e., reused or did not use enfuvirtide), and excluding the patients who discontinued for other reasons than virological failure (n=406). The subgroup using de novo enfuvirtide was excluded to avoid any confounding effect of using a new ARV class
- Virological response at Week 24 is presented relative to the response achieved by the subgroup of patients without detectable NNRTI RAMs at baseline* (n=52; relative response=1.0)
- Decreased virological response was defined as a response that was at least 25% lower than that of the subgroup of patients without detectable NNRTI RAMs at baseline, using the primary efficacy endpoint of confirmed viral load <50 HIV-1 RNA copies/mL
- RT mutations were included in the analysis if they were present at baseline in five or more patients

*patients had NNRTI RAMs from previous genotype

List of NNRTI RAMs evaluated (N=44)

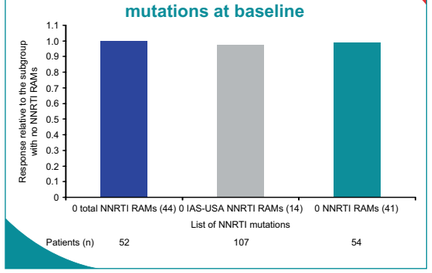
V90I	A98G	L100I	K101E	K101P	K101Q	K103H	K103N	K103S	
K103T	V106A	V106I	V106M	V108I	E138G	E138K	E138Q	V179D	
V179E	V179F	V179G	V179I	Y181C	Y181I	Y181V	Y188C	Y188H	
Y188L	V189I	G190A	G190C	G190E	G190Q	G190S	H221Y	P225H	
F227C	F227L	M230I	M230L	P236L	K238N	K238T	Y318F		

IAS-USA NNRTI RAMs; Additional NNRTI RAMs

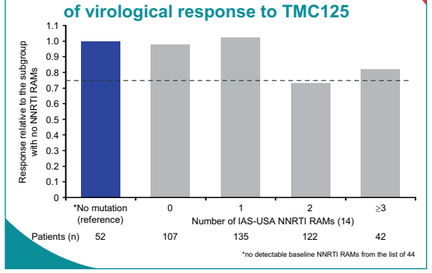
- 14 IAS-USA NNRTI RAMs[1]
- 27 additional NNRTI RAMs[2]
- 3 additional NNRTI mutations associated with an increased TMC125 FC by linear regression analysis of 3,255 baseline isolates

[1]Johnson, et al. Top HIV Med 2006;14:125–30
[2]Tambuyzer, et al. EHDRW 2007; Rimsky, et al. IHDRW 2007

Similar virological responses in patients with no detectable baseline NNRTI mutations at baseline

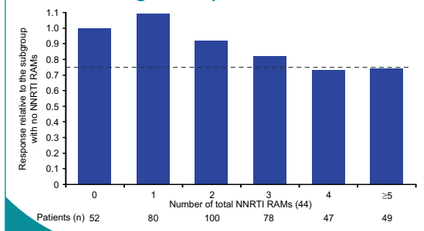


The number of baseline IAS-USA NNRTI RAMs (14) is not a good predictor of virological response to TMC125



*no detectable baseline NNRTI RAMs from the list of 44

The number of baseline total NNRTI RAMs (44) is not a good predictor of virological response to TMC125



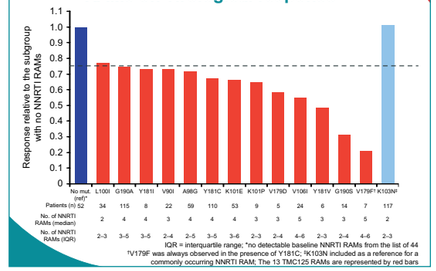
List of TMC125 RAMs

V90I	A98G	L100I	K101E	K101P	K101Q	K103H	K103N	K103S
K103T	V106A	V106I	V106M	V108I	E138G	E138K	E138Q	V179D
V179E	V179F	V179G	V179I	Y181C	Y181I	Y181V	Y188C	Y188H
Y188L	V189I	G190A	G190C	G190E	G190Q	G190S	H221Y	P225H
F227C	F227L	M230I	M230L	P236L	K238N	K238T	Y318F	

NNRTI RAMs present in ≥5 patients; TMC125 RAMs

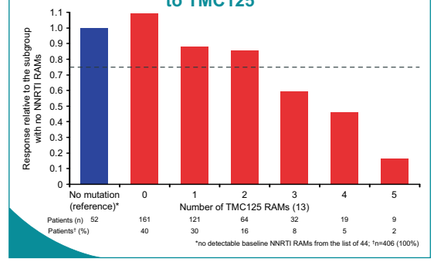
- 44 NNRTI RAMs were studied
- 26 NNRTI RAMs were present in ≥5 patients
- 13 TMC125 RAMs were identified at baseline to have an impact on virological response

The effect of baseline TMC125 RAMs on virological response



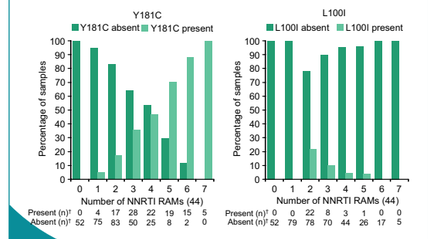
IQR = interquartile range; *no detectable baseline NNRTI RAMs from the list of 44
†V179F was always observed in the presence of Y181C; ‡K103N included as a reference for a commonly occurring NNRTI RAM; The 13 TMC125 RAMs are represented by red bars

The number of baseline TMC125 RAMs correlated with the virological response to TMC125



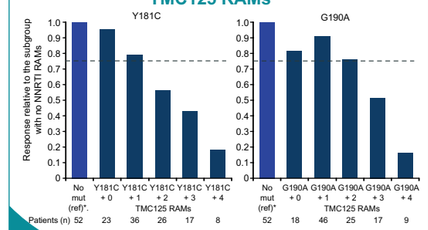
*no detectable baseline NNRTI RAMs from the list of 44; †n=406 (100%)

Some mutations* are present in isolates with more NNRTI RAMs



*A98G, K101E, Y181C, V179F, G190A; †n=number of patients

Decreased virological response is only observed with multiple concomitant TMC125 RAMs

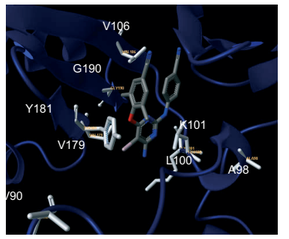


*no detectable baseline NNRTI RAMs from the list of 44

Multivariate analysis of the effect of TMC125 RAMs on virological response

- The effect of the number of TMC125 RAMs on the virological response was analysed in a multivariate logistic regression model
- The data showed that the effect of the TMC125 RAMs on the virological response was highly statistically significant (p=0.0008), when corrected for the baseline viral load, baseline CD4 cell count, baseline number of sensitive antiretrovirals in the regimen, and the baseline FC for DRV

Positioning of TMC125 and the TMC125 RAMs in the NNRTI binding pocket of the HIV-1 RT



Conclusions

- Using the pooled data from DUET-1 and DUET-2, 13 baseline RT mutations were associated with resistance to TMC125
  - V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, G190S
  - 70% of patients had no or only one TMC125 RAM
  - 15% of patients had ≥3 TMC125 RAMs
  - the TMC125 RAMs mainly occurred in the presence of other NNRTI RAMs.
- An increasing number of baseline TMC125 RAMs was associated with a decreasing virological response to TMC125
  - this effect was highly statistically significant in a multivariate analysis correcting for baseline parameters such as viral load, phenotype sensitivity score and DRV FC
  - the largest impact on virological response was observed in the subgroups of patients with three or more TMC125 RAMs.
- These pooled data from the Phase III DUET trials in treatment-experienced patients with HIV-1:
  - identify the baseline genotypic determinants of decreased virological response to TMC125
  - provide guidance in the interpretation of genotypic resistance data related to TMC125.

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