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[PL5.6] IMPACT OF NNRTI AND NRTI RESISTANCE ON THE RESPONSE TO THE REGIMEN OF TMC125 PLUS TWO NRTIS IN STUDY TMC125-C227

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B Woodfall, J Vingerhoets, M Peeters, I Peeters, G De Smedt, GD Miralles, M.P. de Béthune
Tibotec BVBA, Mechelen, Belgium

PURPOSE OF THE STUDY: TMC125 is a novel NNRTI with antiviral activity against NNRTI-resistant HIV-1. TMC125-C227 was an exploratory Phase II trial comparing TMC125 and a PI, given with two NRTIs, in NNRTI-resistant but PI-naïve patients after first-line NNRTI failure.

METHODS: Patients with evidence of NNRTI resistance were randomized to TMC125 ($N=59$) or an investigator selected PI ($N=57$) with a backbone of 2 investigator-selected, sensitive NRTIs. Treatment with TMC125 was prematurely discontinued due to suboptimal virologic response compared to control.

SUMMARY OF RESULTS: At baseline, median number of NNRTI mutations was 2 (range 0-4) and median fold change (FC) to TMC125 was 2.0. Median number of NRTI mutations was 1 (range 0-7), 9% and 12% of subjects in TMC125 and control groups, respectively, did not receive two sensitive NRTIs. Patients with higher TMC125 FC also frequently had higher numbers of NNRTI and NRTI mutations. For patients reaching week 12, 57% and 91% achieved at least 1 \log_{10} viral load decline in TMC125 and control groups, respectively. PK, baseline CD4 and viral load were not associated with virologic response. In contrast, increased numbers of NRTI and NNRTI mutations, use of inactive NRTIs, and higher TMC125 FC were associated with virologic failure.

CONCLUSIONS: In this study, in PI-naïve patients having failed a first-line NNRTI regimen, the level of NNRTI and NRTI resistance was higher than expected. Since patients were PI naïve, these higher levels of baseline resistance probably account for the difference in outcome between the TMC125 and PI arms. Given the demonstrated long-term virological benefit of TMC125 in patients with NNRTI and PI resistance, evaluation of TMC125 in NNRTI and PI experienced patients continues in ongoing Phase III trials.

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