

## **Single-nucleotide polymorphisms ABCB1 3435C>T, 1236C>T and CYP2B6 516G>T predict higher plasma concentrations of nevirapine (NVP)**

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**Background:** Nevirapine (NVP) is widely used in naïve patients worldwide. Minimum effective concentration (MEC) of NVP is known to be 3400 ng/ml. However, our group previously described a higher C<sub>trough</sub> cut off (4300 ng/ml) associated with lower probability of selection of NVP-associated primary resistance mutations (NVP-PRMs) in case of virological failure. Since activity of both transporters (P-Glycoprotein) and metabolic enzymes (CYP450 isoform 2B6 and 3A4) may influence NVP plasma concentrations, we evaluated whether single-nucleotide polymorphisms (SNPs) in these genes may work as predictors of NVP exposure above 4300 ng/ml.

**Materials and Methods:** Patients were recruited in Torino. Patients administered with NVP plus 2 N(t)RTIs since at least 3 months were considered in the study. Sampling was performed after written informed consent was obtained in accordance with local ethics committee indications. Main inclusion criteria were, no concomitant interacting drugs, no hepatic or renal function impairment, self-reported adherence > 95%. NVP C<sub>trough</sub> was measured in samples collected 10-14 h after dosing by a validated HPLC-PDA method. Genotyping was conducted by real time PCR based allelic discrimination using standard methodology. Statistical analysis was conducted by Mann Whitney or Spearman Rank to assess the effects of weight, age, gender, and genotype on NVP C<sub>trough</sub>. Median value of individual measurements was considered. Values were expressed as ng/ml

**Results:** 108 patients met the inclusion criteria. Median number of C<sub>trough</sub> measurement for patients was ( $\pm$ SD) 1.59 ( $\pm$ 0.85). No associations between weight, age, gender and NVP C<sub>trough</sub> were observed. The mean of median NVP C<sub>trough</sub> in individuals with mutant allele (GT or TT, n=54) for CYP2B6 516 was higher as compared to patients wild-type genotype (GG, n=54) [5624 ( $\pm$ 1812) vs 4468 ( $\pm$ 1568), respectively, p=0.001]. These two genetic groups were then subdivided based on the presence of at least one of ABCB1 3435 and 1236 homozygote mutate genotype (3435CC/CT+1236CC/CT vs 3435TT/1236TT) and finally four groups were identified:

GG/3435CC/CT + 1236CC/CT (group 1), GG/3435TT/1236TT (group 2), GT-TT/3435CC/CT + 1236CC/CT (group 3), and GT-TT/3435TT/1236TT (group 4).

A significant positive correlation between level of NVP C<sub>trough</sub> and genetic group was observed, ( $p=0.373$  p<0.001). Forty-three percent of the patients in group 1, 86% in group 2, 73% in group 3, and 97% in group 4 showed NVP C<sub>trough</sub> above the suggested cut-off value of 4300 ng/ml. In multivariate logistic regression analyses, being in group 2 or higher was shown to be the only independent predictor of NVP C<sub>trough</sub> above 4300 ng/ml (OR = 3.53, 95% CI 1.48 to 8.43; p = 0.004).

**Conclusions:** These findings suggest that the combined effect of CYP2B6 516G>T and ABCB1 3435C>T plus 1236 C>T may actually determine an important influence on NVP plasma exposure and therefore on the likelihood of achieving a C<sub>trough</sub> above 4300 ng/ml, a previously suggested cut off of lower probability of selection of NVP-PRMs. Further clinico-pharmacologic studies are now required to confirm this association and to see whether the best candidates to NVP therapy may be identified by relying upon such pharmacogenomic approach.

*No conflict of interest*