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Potential implications of CYP3A4, CYP3A5 and MDR-1 genetic variants on the efficacy of Lopinavir/Ritonavir (LPV/r) monotherapy in HIV-1 patients

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Introduction: Several genetic single nucleotide polymorphisms (SNPs) in biotransformation enzymes (CYP3A4, CYP3A5) or transporter proteins (multidrug resistance MDR1 gene product, P-gp) are involved in PI metabolism so that PI pharmacokinetics is characterized by a large inter-individual variability. The aim of this study was: (i) to develop an in-house PCR/direct sequencing, based on DNA purification of full-length CYP3A4 and CYP3A5 genes (SNPs) and MDR1 C3435T variant; (ii) to investigate association of CYP3A4 and CYP3A5 reported or unreported genetic polymorphisms and MDR1-C3435T (CC homozygote, CT heterozygote, TT homozygote) with clinical outcome of HIV-1 infected subjects treated with PI.
Methods: Overall, 39 HIV-1 infected patients receiving boosted Lopinavir (LPV/r) monotherapy after virological suppression were genotyped and analyzed through PCR and direct sequencing of full-length CYP3A4 and CYP3A5 gene sequences [1] and MDR1 gene (C3435T). CD4+T-cell counts and plasma viral load were analyzed before and after LPV/r initiation; LPV/r therapeutic drug monitoring (TDM) was determined at 12-hours.
Results: LPV/r TDM (ng/ml) did not show significant differences among CYP3A4 or CYP3A5 SNPs, although a mean lower level of LPV/r was associated with detection of several SNPs: CYP3A5*3 rs776746; CYP3A5 rs28365088, CYP3A5 rs15524, CYP3A4 rs2687116, and a not already described polymorphism CYP3A4 nt20338. In follow-up analysis, $<90\%$ adherence was the main factor associated with virological failure of LPV/r monotherapy (83.3% of failure vs 34.4%, $p<0.001$ at log-rank test). Adjusting for adherence, the detection of a single CYP3A5*3 rs776746 and CYP3A5 rs15524 SNPs was associated with higher probability of LPV/r monotherapy failure ($p<0.01$), and in general, detection of any CYP3A5 SNP was associated with failure (26.2% vs 58.3%, $p=0.067$). No-association with detection of any CYP3A4 SNPs was found. MDR1 TT variants showed significant lower frequency of treatment failure (0.0% vs 47.7%, $p=0.026$), since non-TT homozygote patient failed LPV/r monotherapy.
Conclusions: Efficacy of PI monotherapy is strongly dependent from patient adherence, but, in adherent patients, genetic factors, such as CYP3A5 and MDR1-C3435T gene variants, may affect the response to treatment, though their role, as well of other genetic variants, need further investigation.

Reference

1. Berno G, Zaccarelli M, Gori C, Tempestilli M, Antinori A, Perno CF, et al. Analysis of single-nucleotide polymorphisms (SNPs) in human CYP3A4 and CYP3A5 genes: potential implications for the metabolism of HIV drugs. BMC Med Genet. 2014;15:76.

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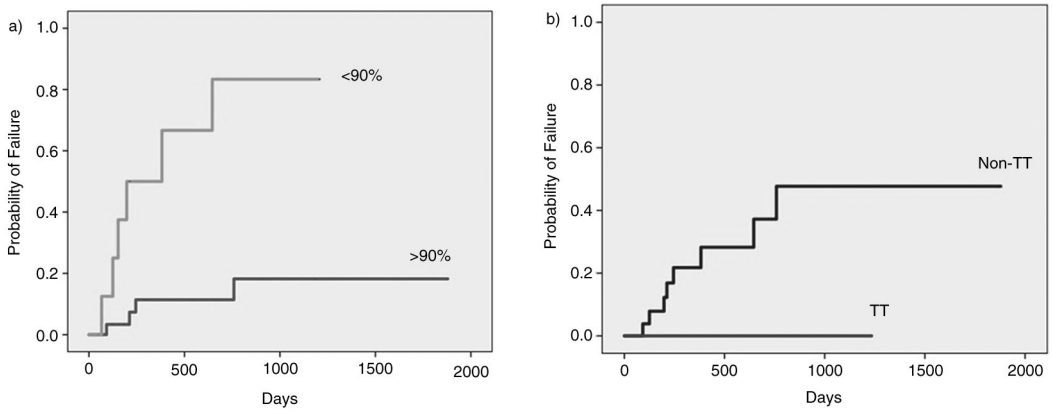

Figure 1. a) Probability of failure of LPV/r monotherapy by treatment adherence; b) Probability of failure of LPV/r monotherapy by MDR1 gene (C3435T).