Effect of renal transporter genetic polymorphisms on linezolid pharmacokinetic

S. Allegra[1], J. Cusato[1], L. Baietto[1], G. Fatiguso[1], A. Ariaudo[1], S. Corcione[1], G. Di Perri[1], F.G. De Rosa[1], A. D'Avolio[1]

[1]Dept. of Medical Sciences, Unit of Infectious Diseases, Amedeo di Savoia Hospital, University of Turin, Italy

Linezolid is an oxazolidinone active against Gram-positive bacteria and it inhibits the mRNA binding to the ribosome. It is a methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumonia,* vancomycin-resistant enterococci and multi-drug resistant tubercolosis therapy option. This drug is not a cytochrome P450 system substrate and it is mainly excreted by kidney. We performeda retrospective study ofplasma linezolidexposure over 24 hs according to single nucleotide polymorphisms (SNPs) in genes involved in renal drug elimination. Fourteen caucasian patients, in the intensive care unit (ICU), treated with intravenous linezolid (600mg twice daily), afferent to San Giovanni Battista Hospital (Turin), were enrolled between 2011 and 2012. Inclusion criteria were: age above 18 years, and no HIV/HCV/HBV infection. Allelic discrimination for SNPs in *MDR1*, *MRP2*, *MRP*, *BCRP1*, *OAT1* and *OCT1 g*eneswasperformed by real-time PCR. Drug plasma concentrationsweremeasuredthrough an UPLC-PDA validated method (Baietto et al., 2013) andarea under the curve over 24 hs (AUC) valuesweredetermined by the mixed log-linear rule, usingKineticasoftware.We found a significant association between *MRP2*-24 rs717620 G>A SNP and AUC/minimum inhibitory concentration (MIC) rate; besides, *MDR1* 3435 rs1045642 C>T variant showed a border-line influence on half-life and minimum serum concentration, whereas *OCT1* 480 rs683369 C>G one seemed to have a role on volume of distribution at steady-state corrected pro-Kg. In linear regression analysis, only *MRP4* 3348 rs1751034 CC genotype was able to predict linezolid AUC/MIC.

Pharmacogenomics and therapeutic drug monitoring could contribute to enhance the antimicrobial therapy optimization on the basis of interindividual genetic variability (Baietto et al., 2014).This study suggests, despite the confounding factors associated to ICU patients, for the first time, the usefulness of genetic-based linezolid therapy and highlights the needed of therapy personalization. However, further studies, in bigger and different cohorts, are required to confirm this data and to clarify the role of the evaluated SNPs in drug pharmacokinetics.

Baietto (2014). *Curr Drug Metab*. 15, 581-598.
Baietto (2013). *J Chromatogr B Analyt Technol Biomed Life Sci*. 936, 42-47.