Demetriou and Kostrikis *Retrovirology* 2010, **7**(Suppl 1):P28
http://www.retrovirology.com/content/7/S1/P28

RETROVIROLOGY

POSTER PRESENTATION Open Access

Implications of hcv natural genetic diversity on HCV NS5B inhibitor NM283

Victoria L Demetriou*, Leondios G Kostrikis

From 16th International Symposium on HIV and Emerging Infectious Diseases
Marseille, France. 24-26 March 2010

Background

The HCV NS5B RNA polymerase is a new target for drug development for HCV disease. Valopicitabine (NM283), the prodrug of 2'-C-Methylcytidine (NM107), has been the most clinically advanced NS5B nucleoside inhibitor. Nucleoside inhibitors exhibit similar activity among genotype 1 strains, but their efficacy among other genotypes is largely unknown. In this study NS5B amino acid polymorphisms in positions affecting activity and drug efficacy were investigated in sequences of all HCV genotypes.

Methods

NS5B amino acid positions significant for catalytic activity, drug binding and resistance were recovered from bibliography and molecular modelling. NS5B sequences were located and downloaded from the HCV sequence database, and added to experimentally derived NS5B sequences from drug-naïve patients in order to analyse significant amino acid positions for natural polymorphisms. The most frequent polymorphisms in resistance-conferring position 282 were further investigated by docking analysis.

Results

The results revealed a highly conserved active site. Natural polymorphisms at position 282 were found at low frequencies, in particular the drug resistant S282T, and S282R, whose effect is unknown. No genotype-specificity of polymorphisms could be confirmed.

Discussion

The selection of S282T as a drug-resistant variant when S282R also exists naturally at the same frequencies implies that the latter may not confer resistance to NM283. Molecular modelling suggests that loss of NM107 activity in the presence of the S282T mutation may be a result from improper alignment of the drug at the active site. Overall, the results imply the need for resistance testing when 2'-C-methyl nucleotide inhibitors are widely available.

Published: 11 May 2010

doi:10.1186/1742-4690-7-S1-P28
Cite this article as: Demetriou and Kostrikis: Implications of hcv natural genetic diversity on HCV NS5B inhibitor NM283. *Retrovirology* 2010 7(Suppl 1):P28.

* Correspondence: victoria.demetriou@ucy.ac.cy
University of Cyprus, Nicosia, Cyprus