

15th International HIV Drug Resistance Workshop



13-17 June 2006, Sitges, Spain

GENOTYPIC ANALYSIS OF THE GAG CA/SP1 CLEAVAGE SITE IN PATIENTS RECEIVING THE MATURATION INHIBITOR PA-457

Antivir Ther. 2006, 11:S37 (abstract no. 32)

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BACKGROUND: PA-457 is a first-in-class HIV maturation inhibitor that specifically blocks cleavage of the CA-SP1 Gag intermediate, preventing the formation of mature CA. Selection for viruses that are resistant to PA-457 *in vitro* resulted in the identification of four *gag* codons (H358, L363, A364, and A366) located proximal to the CA-SP1 cleavage site that affect sensitivity to the drug. Here we describe the genotypic analysis of virus from patient samples collected during two proof-of-concept monotherapy trials with PA-457: a Phase I/II single dose study and a Phase IIa 10-day multiple dose study.

METHODS: A Gag genotyping assay was developed using primers designed to anneal to conserved regions of *gag* flanking the CA-SP1 cleavage site. Patient plasma samples were collected on days 1 (pre-dose), 7, 10, and 28 (end of study) for the Phase I/II single dose study and on days 1 (pre-dose), 5, 11, and 38 (end of study) for the Phase IIa 10-day multiple dose study.

RESULTS: The CA-SP1 cleavage site in Gag was genotyped for 24 patients in the Phase I/II study and 32 patients in the Phase IIa study. None of the changes in the CA-SP1 region associated with resistance to PA-457 *in vitro* were found to emerge in any of the patients by population sequencing. This was consistent with the lack of viral load rebound during the dosing period. Other sequence changes were observed in a few individuals in the Phase IIa study, however these changes do not appear to be treatment related.

CONCLUSIONS: No known PA-457 resistance mutations were observed in any of the 56 patients studied by population genotyping up to 28 days after the final dose. This is despite the fact that, due to the long half-life of PA-457, patients were exposed to sub-

optimal drug concentrations for up to three weeks after completion of dosing, thus increasing the potential for resistance development. This suggests that there may be a fitness cost associated with the resistance mutations identified *in vitro*. PA-457 differs from drugs such as nevirapine and enfuvirtide to which resistance can develop rapidly *in vivo* during monotherapy. Future studies will determine whether PA-457 resistance emerges after more prolonged treatment.

2006-06-13
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