

15th International HIV Drug Resistance Workshop



13-17 June 2006, Sitges, Spain

SELECTION AND CHARACTERIZATION OF MUTATIONS CONFERRING RESISTANCE TO A HCV RNA DEPENDENT RNA POLYMERASE INHIBITOR *IN VITRO*

Antivir Ther. 2006, 11:S6 (abstract no. 4)

A Molla, L Lu, P Krishnan, R Pithawalla, T Dekhtyar, T Ng, W He, T Pilot-Matias, W Jiang, Y Liu, G Koev, K Stewart, D Larson, T Bosse, W Kati, R Wagner, D Kempf and H Mo

Abbott Laboratories, Abbott Park, IL, USA

BACKGROUND: A-848837 is a novel specific inhibitor of the HCV RNA-dependent RNA polymerase with excellent PK in animals. Given the high mutation and replication rate of HCV, it is likely that mutant viruses with decreased susceptibility to antiviral regimens will emerge during therapy. Understanding the *in vitro* resistance profiles of the HCV inhibitors is therefore of considerable interest.

METHODS: The anti-HCV activity of A-848837 was determined in HCV replicon cells by the reduction of HCV RNA. HCV replicon colonies resistance to the inhibitors were selected by treating the HCV subgenomic 1b-N replicon cells with A-848837 at a concentration 10 times above its corresponding IC_{50} in the presence of neomycin. Genotypes of the resistant colonies were determined by sequencing the NS5B polymerase gene. Individual mutations were introduced into a luciferase-expressing replicon by site-directed mutagenesis. The susceptibility of the mutants was evaluated by a trans-replication assay.

RESULTS: A-848837 displayed potent activity in the HCV replicon tissue culture with an IC_{50} of 2 and 4 nM against genotypes 1b and 1a, respectively. Following selection with A-848837, replicon colonies were found to be approximately 33- to >800-fold resistant to A-848837. Each colony contained one to three of the following mutations: G46A, S368T, I392F, M414T, Y448H, Q514R, G554D, D559G and Y586C within NS5B polymerase gene. Molecular clones containing the above single amino acid substitutions displayed 4- to 255-fold reduced susceptibility to A-848837. In contrast, all mutants retained full susceptibility to the polymerase inhibitor thiophene-2-carboxylic

acid (Shire polymerase inhibitor), HCV protease inhibitor and interferon (IFN). Furthermore, combination of A-848837 with IFN or protease inhibitor produced an additive to synergistic effect in replicon cells. All mutants except I392F exhibited reduced replication capacity compared to the wild-type replicon.

CONCLUSIONS: This study suggested that single amino acid substitutions at any of several positions could result in reduced susceptibility to A-848837. However, combination of this inhibitor with IFN or protease inhibitor may be synergistic in controlling HCV replication.

2006-06-13
4

Copyright © 2006 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.