

14th International HIV Drug Resistance Workshop



7-11 June 2005, Québec City, Canada

PREVALENCE AND IMPACT OF PROTEASE CODON 33 MUTATIONS/POLYMORPHISMS IN TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS ENROLLING IN CLINICAL TRIALS

Antivir Ther. 10, Suppl 1:S28 (abstract no. 26)

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BACKGROUND: Protease gene mutations at codon 33 have been associated with resistance to some but not all protease inhibitors (PIs). Little is known about the difference in prevalence of codon 33 mutations/polymorphisms between treatment-naïve and treatment-experienced patients, and the effect of codon 33F on PI resistance patterns.

METHODS: Baseline genotypes (TRUGENE) from 772 patients participating in two different randomized clinical trials (504 antiretroviral (AR) treatment-naïve patients (FIRST-CPCRA 058) and 268 AR treatmentexperienced patients (MDR-CPCRA 064) were evaluated for the presence of protease codon 33 mutations/polymorphisms. Baseline phenotypes (Antivirogram), including fold-change in resistance for 16 AR drugs, were available for the 268 treatmentexperienced patients. Multivariate linear regression models were used to determine factors associated with phenotypic fold-change for PIs.

RESULTS: The prevalence of codon 33 mutations/polymorphisms was 5.2% in the naïve cohort (0.2% 33F, 2.5% 33V, 2.5% 33I) and 34.7% in the experienced cohort (30.2% 33F, 1.5% 33V, 3.0% 33I). In the AR-experienced cohort (mean=4.2 prior PIs, 10.6 prior AR drugs overall), a model adjusting for the number of protease mutations present, the presence of specific major protease mutations, and prior PI drug exposure (current, prior only, never) was used to estimate the phenotypic fold-change in resistance for those with and without mutation 33F. Those with 33F had a significantly higher fold-change for amprenavir (25.7 vs 7.6, $P<0.0001$) and ritonavir (163 vs 96.8, $P=0.003$), but

lower fold-change for indinavir (17.4 vs 28.6, $P=0.04$). The fold changes for nelfinavir, lopinavir and saquinavir were not significantly different; resistance testing for atazanavir and tipranavir was not available.

CONCLUSIONS: At protease codon 33, the prevalences of polymorphisms 33V and 33I were similar for PI-naïve and PI-experienced patients (<3%), but the prevalence of 33F was significantly different (0.2% vs 30.2%). In the treatment-experienced cohort, the differences between those with and without 33F in phenotypic fold-change for amprenavir, indinavir, and ritonavir persist after adjustment for the presence of other major PI mutations and PI drug exposure history. Given the availability of newer PIs that may select for 33F, monitoring for the presence of this mutation should be ongoing for both treatment-naïve and treatment-experienced patients.

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2005-06-07
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