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Impact of the HIV-1 protease N88S substitution on protease inhibitor susceptibility and clinical response

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Purpose of the study

N88S in HIV-1 protease is a major atazanavir (ATV) resistance mutation (IAS-USA 2008), but there are limited clinical data on its prevalence and on its impact on susceptibility to ATV and other protease inhibitors. We conducted a systematic analysis of N88S in treatment-naive studies of ATV.

Methods

We reviewed all BMS-sponsored studies of ATV in HIV-infected treatment-naive adults for occurrences of N88S. For each case, we describe the clinical course and genotypic and phenotypic resistance patterns.

Summary of results

Of 1,736 subjects treated with ATV in five randomized controlled trials and one observational study, we identified 11 subjects with N88S. Of the 10 with a matched phenotype available, one subject had N88S at baseline only, and nine had N88S emerge on treatment at virologic failure: five on ATV without ritonavir (RTV), three on ATV/RTV, and one on ATV/RTV after prior ATV without RTV. Phenotype (Monogram Biosciences) for ATV ranged from 1.26 to 27 FC (fold-change from wild-type) and was below the clinical cutoff (5.2) for ATV/RTV in 6/10 cases. Virus remained susceptible to amprenavir, darunavir, lopinavir, and tipranavir in all cases where susceptibility to the drug was included in the phenotype assay. Clinical response data on ATV were available for two subjects. The subject with N88S at baseline (ATV FC 1.38) proceeded to confirmed virologic suppression (HIV-RNA <50 c/mL) on tenofovir, emtricitabine, and ATV/RTV and remained suppressed through 96 weeks of treatment. Another subject developed N88S on the same regimen at week 16 (ATV FC 3.71) but virologically resuppressed (HIV-RNA <50 copies/mL) through 96 weeks without a change in regimen.

Conclusion

Emergence of the N88S substitution in HIV-1 protease is rare in antiretroviral-naive patients treated with an atazanavir-containing regimen. Virus with N88S often remained susceptible to ATV/RTV and was consistently susceptible to other commonly-used protease inhibitors.