Limited cross-resistance to TPV in patients previously treated with two or more protease inhibitors

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Abstract

Purpose of the Study

Efficacy of protease inhibitor (PI) regimens is limited by PI cross-resistance. Tipranavir (TPV) is active against PI-resistant HIV-1. RESIST II showed that highly treatment-experienced (HTE) patients taking TPV had substantially greater responses than patients taking comparator PIs. Baseline PI cross-resistance patterns were evaluated.

Methods

520 baseline HIV-1 isolates from HTE patients in RESIST II and 1162.51 studies were analyzed for phenotypic drug resistance to TPV, lopinavir (LPV), atazanavir (ATZ), saquinavir (SQV), indinavir (IDV), nelfinavir (NFV) and amprenavir (APV) using Antimicrobial Software. For evaluation of cross-resistance, fold change (FC) in Copy Number of Clinically significant resistance was determined for 4 PI, APV, SQV, IDV, NFV, ATZ, and 40 LPR.

Results of Summary

5% isolates were resistant to LPV, APV, SQV, IDV, NFV, ATZ, and TPV. There was a weak positive association between resistance to other PIs and susceptibility to TPV. APV-27% isolates resistant to TPV pre-defined at ≤ 4 for all except LPV (judged 4).

Conclusions

TPV maintains significant antiretroviral activity (FC 0.44-fold) against majority of HVI clinical isolates resistant to the PI. High level resistance to TPV (>10-fold) is uncommon (0.2%) in viruses from HTE patients who have taken 2 PI.

Introduction

Protease inhibitors (PIs) have significantly impacted the morbidity and mortality of HIV disease progression since their introduction into the medical market in the late 1990s. As PI are potent agents, however, the efficacy of PIs has been shown to be multi-target, leading to the appearance of drug resistant viral variants.

Intronator (TPV) is a novel, non-protease inhibitor of the human immunodeficiency virus (HIV) PI.

It has been shown that TPV retains activity against more than 90% of PI-resistant resistant viral isolates. Decreased susceptibility to TPV (defined as ≥ 4-fold wild-type [WT] APV) was associated with multiple protease mutations, which included two or less of the major, and were shown to be multi-target, leading to the appearance of drug resistant viral variants.

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Resistance testing with VIRCO ANTIVIROGRAM™ assay produced an IC 50 fold change from treatment-naive viruses ≥ 8 IAS mutations were required to achieve phenotypic resistance to TPV (>4-fold IC 50), due to large numbers of isolates resistant to the comparator PI but susceptible to TPV.

The low correlations ranging between 23 and 42% are primarily due to large numbers of isolates resistant to the comparator PI but susceptible to TPV.

Methods

Baseline isolates from the Phase 3 TPV program (NCTs: 1162.51 RESIST II, 1162.46 RESIST II, and 1162.51) that were assessed both phenotypically and genotypically were the basis for the analysis (n=326). Patients in these trials had previously been treated with at least 2 commercially available PIs, and had failed treatment with ≥2 PIs and ≥4 PIs (Table 1). The low correlations ranging between 23 and 42% are primarily due to large numbers of isolates resistant to the comparator PI but susceptible to TPV.

Results

Over 75% of patients had viral RNA resistant to the first generation PIs, while 73% had virus susceptible to TPV (Table 1). These correlations range between 22 and 64% and are primarily due to large numbers of isolates resistant to the comparator PI but susceptible to TPV.

TPV susceptible viruses had few mutations but still had a median of 10–12 mutations. At least 8 mutations were required to achieve phenotypic resistance to TPV (>4-fold). More than 50% of TPV resistant viruses had 10 or more mutations (Figure 7). TPV susceptible viruses had few mutations but still had a median of 10–12 mutations. Even with 16–17 TPV resistant mutations, some IAS-resistant viruses remained susceptible to TPV.

Conclusions

TPV maintains phenotypic susceptibility (FC 0.44-fold) against the majority of HIV-1 clinical isolates resistant to other PI. High level resistance to TPV (>10-fold) is uncommon (0.2%) in viruses from HTE patients who have taken 2 PI.

References


To aid in analysis of distribution of isolates a vertical line is inserted corresponding to a TPV change from wild-type ≤ 4 or a horizontal line was inserted corresponding to a change from wild-type 4 for the commercially available PIs except LPV for which a 40-fold wild-type line was used.

To evaluate genotypic and phenotypic correlation, IAS mutations [5] were analyzed individually and the percentage of isolates resistant to the comparator PI, but not TPV to resistant to both commercial PI and TPV was calculated (Table 2). Further, the number of IAS mutations was depicted for each commercially available PI and compared to TPV (Figure 7). IAS mutation scores are calculated as the number of amino acid positions with one or more mutations from the type for TPV (x-axis) and for the commercially available PI (y-axis).

The blue highlighted rows show mutations which have disproportionately higher difference between TPV-S/CPI-R and TPV-R/CPI-R viruses was observed.

The orange highlighted rows represent mutations at which disproportionately higher difference between TPV-S/CPI-R and TPV-R/CPI-R viruses was observed.

The green highlighted rows represent mutations at which disproportionately higher difference between TPV-S/CPI-R and TPV-R/CPI-R viruses was observed.

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