Better treatment response (TR) to tipranavir/r (TPV/r) compared to lopinavir/r (LPV/r) in patients with higher lopinavir (LPV) mutation scores

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Poster Number P197
Eighth International Congress on Drug Therapy in HIV Infection
Glasgow, UK, 12–16 November 2006

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Abstract

Significantly more patients (pts) had a TR with TPV/r than a comparator PI/r in RESIST. We compared Week 48 TPV/r and LPV/r TRs in pts whose baseline (BL) isolates had different LPV scores to identify protease mutations that unduly affect LPV/r activity vs. TPV/r.

Pts had ≥3-class ARV experience; ≥2 prior PIs; ≥1 primary PI mutation; ≤2 mutations at 33, 82, 84, 90. BL resistance and Wk 48 TRs in LPV/r stratum pts randomised to TPV/r or LPV/r were compared.

We analysed LPV/r stratum pts not taking LPV/r at screening and randomised to TPV/r (164) or LPV/r (150). Median BL characteristics were similar: 171 CD4 cells/mm^3; 4.7 $\log_{10}$ c/mL VL; LPV score: 5. 75 phenotyped isolates: median FC in IC_{50} to TPV/LPV were 0.7/1.4 if LPV score 0–3; 1.9/17.8 if 4–5; 1.9/41.3 if 6–7; 2.7/94.5 if >7.

Wk 48 TRs were similar in pts (72) whose isolates had 0–3 LPV mutations. Pts whose isolates had 4–5 (95) or 6–7 (117) LPV mutations had better TRs to TPV/r. In the TPV/r arm, 54% (44%) had VL <400 (<50) vs. 39% (27%) in LPV/r pts whose isolates had 4–5 LPV mutations. If isolates had a LPV score of 6–7, VL <400 (<50) was 32% (26%) for TPV/r; 19% (13%) for LPV/r. Median VL reductions in pts with 4–5 or 6–7 LPV mutations were 1.9 or 0.5 TPV/r; 1.2 or 0.3 LPV/r.

As LPV scores increased (>3), phenotypic resistance level increased more for LPV than TPV. Week 48 TRs were greater in patients taking TPV/r vs. LPV/r. In patients whose BL isolates were genotypically LPV sensitive but had >3 LPV score mutations, virologic responses were better with TPV/r.

Introduction

Tipranavir (TPV/r, Aptivus®), a new generation protease inhibitor (PI), is being evaluated in the RESIST 1 and 2 studies, which are two randomised, ongoing, open label, comparative Phase III trials [1,2]. TPV exerts potent activity against multiple PI-resistant HIV-1 *in vitro*. TPV/r has been shown to be effective and well tolerated in patients who have taken ≥2 PI-based regimens [1–5].

Triple antiretroviral (ARV) class experienced patients were enrolled in the RESIST studies and were followed for at least 96 weeks. They were randomised to receive an optimised background regimen (OBR) plus TPV/r or a standard of care, ritonavir boosted, comparator PI (CPI/r) selected by genotype. Given the similar study designs of RESIST 1 and 2, the data were combined for analysis. TPV/r was superior to CPI/r in virological and immunological responses in highly treatment experienced (HTE) patients at Weeks 24, 48 and 96 of the RESIST studies [1,2].

In this study, we compared Week 48 treatment responses (TRs) to TPV/r and to lopinavir/r (LPV/r) in patients whose baseline (BL) isolates had different LPV genotypic mutation scores in order to identify the impact of this score on the activity of LPV/r compared to that of TPV/r.

Study design

RESIST 1 and 2 enrolled male and female patients with HIV infection who fulfilled the following entry criteria:

- ≥18 years old
- ≥3 consecutive months' experience with 3 classes of antiretroviral (ARV) drugs (NRTIs, NNRTIs, PIs)
- ≥2 PI-based regimens for ≥3 months; one of which was the current treatment regimen
- Any CD4 cell count
- Viral load (VL) ≥1000 copies/mL
- Viral isolate carrying ≥1 primary protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M
- Viral isolate carrying ≤2 mutations at codons 33, 82, 84, 90.

The investigators selected the CPI/r (lopinavir/r, indinavir/r, saquinavir/r or amprenavir/r) and the OBR prior to randomisation. The use of enfuvirtide (ENF) was allowed; patients were stratified by the planned use of ENF, as well as by the pre-selected CPI/r (the CPI/r stratum). Patients were then randomised to receive 500/200 mg TPV/r or standard doses of the CPI/r plus approved doses of the components of the OBR.

After Week 8, patients who failed virologically in the CPI/r arm were able to receive TPV/r prior to its regulatory approval via a long term safety study, provided that there was documented evidence that they had been adherent to their study medication.

Baseline resistance profiles for patients assigned to the LPV/r stratum and who were not taking LPV/r at screening were evaluated. Treatment response (TR) rates (confirmed VL reduction ≥1 $\log_{10}$ copies/mL at Week 48 without viral rebound [confirmed VL <1 $\log_{10}$ copies/mL below baseline]), time to treatment failure (TTF), and the proportions of patients with viral loads (VL) <400 and <50 copies/mL at Week 48 were determined for patients in the LPV/r stratum who were not taking LPV/r at screening and were randomised to receive either TPV/r or LPV/r.

The LPV score is the number of positions in the protease with mutations, from positions 10FIRV, 20MR, 24I, 46IL, 53L, 54LTV, 63P, 71TLV, 82AFT, 84V, 90M [6]. Virus from patients with a LPV score <6 is considered sensitive to LPV/r; scores of 6–7 denote intermediate sensitivity; and scores >7 reflect resistance.

Results

Patient population

The baseline characteristics were similar in both treatment arms of the LPV/r stratum (Table 1). These patients were not taking LPV/r at screening for the RESIST studies: 64% (201/314) had never taken LPV/r; 3.5% (11/314) had taken LPV/r for less than one month; 7.0% (22/314) had taken LPV/r for 1–≤6 months; and 25.5% (80/314) had taken LPV/r for >6 months in the past. The median BL characteristics were: 171 CD4 cells/mm^3; viral load (VL) 4.7 $\log_{10}$ copies/mL; and a LPV score of 5.

Table 1: Baseline characteristics of RESIST 1 and 2 patients in the LPV/r stratum who were not taking LPV/r at screening (Intent to treat non-completer = failure [ITT NCF] population)

Baseline characteristics	TPV/r* (n=164)	LPV/r* (n=150)
Median VL ($\log_{10}$ copies/mL) [range]	4.53 [2.34–6.04]	4.71 [3.03–6.76]
Median CD4 cell count (cells/mm^3) [range]	181 [1–1893]	140 [2–945]
Median LPV mutation score	5	6
LPV mutation score by strata n/N (%)		
0–3	42/164 (25.6)	30/150 (20.0)
4–5	54/164 (32.9)	41/150 (27.3)
6–7	53/164 (32.3)	64/150 (42.7)
>7	15/164 (9.1)	15/150 (10.0)

*All patients also took an OBR.

Phenotypic data were available for 75 isolates (LPV IC_{50}) and for 76 isolates (TPV IC_{50}) (Table 2).

Table 2: Median fold changes in IC_{50} to TPV and LPV stratified by LPV mutation

LPV mutation score	FC in IC_{50} to TPV	FC in IC_{50} to LPV
0–3	0.7	1.2
4–5	1.8	17.8
6–7	1.5	41.4
>7	2.7	94.6

Week 48 responses in LPV/r stratum patients†

Week 48 responses in LPV/r stratum patients who were not taking LPV/r at the time of screening for the RESIST studies were analysed. TRs at Week 48 were similar in the 72 patients taking either TPV/r or LPV/r and whose isolates carried 0–3 LPV mutations (Table 3). As the number of LPV score mutations increased (4–5 [n=95], 6–7 [n=117] or >7 [n=30]), TRs to TPV/r were superior compared to those to LPV/r (Table 3).

Table 3: Week 48 virological responses in LPV stratum† stratified by LPV mutation score

LPV mutation score	TPV/r (n=164) TR (%)	TPV/r (n=164) % VL <400 copies/mL	TPV/r (n=164) % VL <50 copies/mL	LPV/r (n=150) TR (%)	LPV/r (n=150) % VL <400 copies/mL	LPV/r (n=150) % VL <50 copies/mL
0–3	19/42 (45.2)	21/42 (50.0)	17/42 (40.5)	15/30 (50.0)	16/30 (53.3)	13/30 (43.3)
4–5	30/54 (55.6)	29/54 (53.7)	24/54 (44.4)	16/41 (39.0)	16/41 (39.0)	11/41 (26.8)
6–7	19/53 (35.8)	17/53 (32.1)	14/53 (26.4)	14/64 (21.9)	12/64 (18.8)	8/64 (12.5)
>7	5/15 (33.3)	5/15 (33.3)	4/15 (26.7)	1/15 (6.7)	1/15 (6.7)	0/15 (0.0)

Table 3 summarises the Week 48 virological responses in the LPV stratum† stratified by LPV mutation score. For patients harbouring isolates with a LPV score >3, i.e. considered sensitive to LPV, the proportions of patients with undetectable VLs were consistently higher in the TPV/r arm compared to the LPV/r arm (Figure 1).

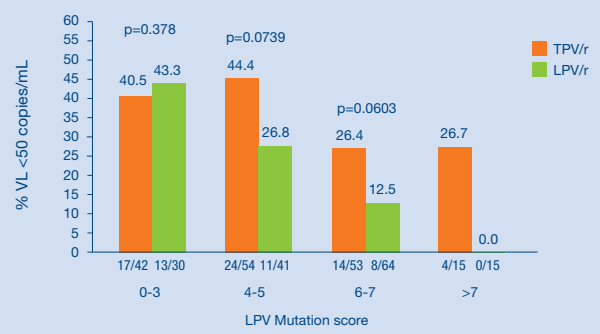

Figure 1: Proportion of patients at Week 48 in LPV stratum† with VL <50 copies/mL, stratified by LPV mutation score

The number of patients in the >7 stratum was too small to calculate a p value.

Median VL reductions in patients infected with HIV carrying 4–5 or 6–7 LPV score mutations were 1.9 $\log_{10}$ copies/mL and 0.5 $\log_{10}$ copies/mL, respectively, in the TPV/r arm. The reductions for the LPV/r arm were1.2 $\log_{10}$ copies/mL and 0.3 $\log_{10}$ copies/mL, respectively.

The genotypic sensitivity scores (GSS) for background RTIs and enfuvirtide were compared for patients taking TPV/r or LPV/r, stratified by LPV mutation score (Table 4). The median GSS was 2 in all groups, except for patients in the TPV/r group with a LPV score >7, where it was 1. There were no significant differences between the groups in terms of GSS, suggesting that the availability of active background drugs was similar for patients in both treatment groups. Hence, it is unlikely that the more favourable responses observed in TPV/r recipients was due to a more active OBR.

Table 4: Genotypic sensitivity to background ARVs stratified by LPV mutation score

	TPV/r				CPI/r			
LPV score:	0–3	4–5	6–7	>7	0–3	4–5	6–7	>7
Genotypic sensitivity to background ARVs (GSS)								
Median	2	2	2	2	1	2	2	2
Subgroups [N (%)]								
0	3 (7.1)	7 (13.0)	7 (13.2)	1 (6.7)	2 (6.7)	6 (14.6)	6 (9.4)	4 (26.7)
1	14 (33.3)	15 (27.8)	15 (28.3)	8 (53.3)	9 (30.0)	13 (31.7)	26 (40.6)	3 (20.0)
2	20 (47.6)	30 (55.6)	23 (43.4)	5 (33.3)	13 (43.3)	14 (34.1)	19 (29.7)	8 (53.3)
≥3	5 (11.9)	2 (3.7)	8 (15.1)	1 (6.7)	6 (20.0)	8 (19.5)	13 (20.3)	0 (0.0)

Conclusions

- Through Week 96, TPV/r was superior to CPI/r in terms of virologic and immunologic efficacy.
- As LPV scores increased (>3), the degree of increased phenotypic resistance was greater for LPV than for TPV.
- Week 48 TRs were greater in LPV/r stratum patients† with LPV scores >3 who were taking TPV/r compared to those taking LPV/r. In patients who had LPV scores <3, responses were similar for TPV/r and LPV/r.
- TPV/r treatment was more likely to achieve undetectable VLs, as recommended in international guidelines [7, 8], than CPI/r in patients† with LPV scores >3.

Acknowledgements

Thanks to all of the patients who took part in RESIST 1 and 2, as well as the investigators at each of the study sites. Boehringer Ingelheim International GmbH sponsored the RESIST studies.

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†Refers to LPV/r stratum patients who were not taking LPV/r at the time of screening for the RESIST studies.