Health-related quality of life and tolerability in treatment-experienced HIV-1-infected patients on tipranavir versus comparator regimens

Supplementary material

Health-related quality of life and tolerability of patients treated in RESIST

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Abstract

Purpose of the Study: To assess health-related quality of life (HRQOL) and adverse events (AEs) in HIV patients on tipranavir boosted with ritonavir (TPV/r) vs. investigator-selected ritonavir-boosted comparator PI (CPI/r) regimens.

Methods: HRQOL was assessed in 1,015 patients using combined data from two randomized, open-label, phase III trials (RESIST 1 and 2). Change in HRQOL was assessed at Week 48 in patients completing the MOS-HIV and analyzed using generalized estimating equations. The MOS-HIV includes Mental Health (MHS) and Physical Health Summary (PHS) and 10 subscale scores. At Week 48, 71% of TPV/r patients remained on treatment vs. 31% on CPI/r. Consequently, reported AEs were exposure-adjusted.

Summary of Results: Occurrence and severity of AEs were associated with lower MOS-HIV scores. Rates of AEs were higher in the CPI/r vs. TPV/r group (562.8 vs. 514.4 per 100 patient-exposure years [PEY], respectively). Treatment-related AEs were more frequent in TPV/r vs. CPI/r patients (75.0 vs. 56.6 per 100 PEY, respectively). TPV/r patients showed positive between group changes vs. CPI/r for MHS (+1.47 points; p<.05), PHS (+0.99), cognitive functioning (+1.04), energy/fatigue (+2.43; p<.05), general health perceptions (+3.53; p<.05), health distress (+2.93; p<.05), mental health (+2.78; p<.05), overall QOL (+2.72; p<.05), pain (+2.19), physical functioning (+1.89), role functioning (+2.83) and social functioning scores (+1.68).

Conclusions: Despite a higher incidence of treatment-related AEs, HRQOL in TPV/r patients was stable or improved in comparison to treatment with CPI/r.

Background

- TPV/r (Aptivus®/r) is a novel non-peptidic protease inhibitor (PI) with potent *in vitro* activity against most HIV-1 strains resistant to currently available PIs.
- TPV/r was approved by the European Medicines Agency (EMEA) and US Food and Drug Administration (FDA) in 2005 for use in highly treatment experienced HIV-1 infected patients [1,2].
- Combined RESIST results showed that TPV/r has a safety profile similar to that of other ritonavir boosted PIs but it is more efficacious since patients on TPV/r were twice as likely to experience a treatment response (defined as confirmed ≥1 $\log_{10}$ copies/mL viral load decrease) at Week 48 compared to patients randomized to CPI/r (33.6% vs. 15.3%; p<0.0001) [3,4].
- The aim of this analysis was to understand the impact of treatment on patient-reported health related quality of life (HRQOL), whilst also taking into account the influence of adverse events (AEs).

Methods

Clinical trials

- RESIST 1 and 2: randomized, open-label phase III trials to compare the efficacy and safety of TPV/r versus CPI/r (amprenavir, fosamprenavir, indinavir, lopinavir or saquinavir combined with ritonavir) in antiretroviral (ARV) treatment experienced patients [3].
- A total of 746 TPV/r patients and 737 CPI/r patients were treated in RESIST 1 (North America and Australia) and RESIST 2 (Europe and Latin America) and followed for at least 48 weeks.
- 486 (65%) of patients on TPV/r and 192 (26%) on CPI/r remained on assigned treatment until Week 48 with a median exposure to study treatment of 384 days in the TPV/r group and 173 days in the CPI/r group.
- Patients enrolled in the RESIST trials were triple ARV class experienced and had been treated with at least 2 previous PI-based regimens.
- Optimized background regimens in RESIST included at least two non-PI ARVs (NRTIs, NNRTIs and/or enfuvirtide).
- Similar design and patient populations permitted pooling of data from the two RESIST trials.

HRQOL data and analysis

- HRQOL was measured in RESIST using the MOS-HIV Health Survey which has been widely used in HIV clinical trials.
- The MOS-HIV is a 35-item, patient administered questionnaire that includes 10 subscales and 2 summary scores [5].
  - Subscales are each scored from 0 to 100 points, with higher scores indicating better health. Mean scores for a reference population are 50 points, with a standard deviation of 10 points.
  - Summary scores are calculated by combining the scores from the subscales into the MHS and PHS summary scores.
- The reliability and validity of the MOS-HIV scales have been well documented with increases in reported symptoms found to correspond to a significant decrease in scores. Responsiveness testing demonstrates that the MOS-HIV detects clinically important changes over time [5–7].
- The MOS-HIV was administered at baseline and at follow-up weeks 8, 16, 24, 40, and 48 at sites in Australia, Canada, France, Germany, Italy, Spain, the UK and the US.
- The pre-specified HRQOL analysis examined the changes in the MOS-HIV summary and subscale scores between the TPV/r vs. CPI/r arms at Week 48 using generalized estimating equations (GEE) regression including MOS-HIV scores at all 6 time points, adjusted for baseline covariates.
- Patients included in the HRQOL analysis were all patients who completed the MOS-HIV at baseline and during at least one follow-up visit.

Tolerability data and analysis

- AEs experienced by patients in the TPV/r and CPI/r group were adjusted for exposure to account for the differential exposure in the two treatment arms.
- To determine how differences in AE incidence between the two treatment arms influence patient HRQOL, GEE analyses were performed to test the association of MOS-HIV scores and patients experiencing AE vs. those experiencing no AEs across both treatment arms. The association was tested for mild, moderate and severe AEs that occurred during a visit window.

Results

- 511 (68%) patients on TPV/r and 473 (64%) patients on CPI/r completed the baseline and at least one-follow up MOS-HIV assessment and were consequently included in the HRQOL analysis.
- The average age of patients included in the HRQOL analysis was 45 years and 44 years in the TPV/r and CPI/r arms, respectively; 88% of patients were male in the TPV/r arm and 91% in the CPI/r arm. Median CD4+ cell counts were 159 and 158 cells/mm^3, respectively. Median viral loads were similar in both groups: 4.8 $\log_{10}$ copies/mL.
- Rates of all AEs were higher in the CPI/r arm vs. the TPV/r arm (562.8 vs. 514.4 per 100 patient exposure years [PEY]) but rates of treatment related AEs were higher in the TPV/r vs. the CPI/r arm (75.0 vs. 56.6 per 100 PEY) (Table 1).
- Mean MOS-HIV scores at baseline differed non-significantly between the two treatment groups, with PHS:49.6 for TPV/r and 50.5 for CPI/r; MHS:47.7 for both TPV/r and CPI/r, and were similar to a reference population.

Table 1. Number (rate per 100 patient-exposure years) of patients with AEs in the HRQOL analysis

	TPV/r	CPI/r
Total treated	511	473
Total AEs	469 (514.4)	397 (562.8)
Mild AEs	422 (287.1)	337 (318.2)
Moderate or severe AEs	372 (167.3)	285 (186.5)
Total drug-related AEs	241 (75.0)	128 (56.6)
Drug-related mild AEs	172 (46.4)	89 (36.4)
Drug-related moderate or severe AEs	145 (34.9)	65 (24.3)
AEs leading to study discontinuation	56 (11.0)	21 (7.1)
Specific AEs (Grade 3–4)		
Diarrhea	31 (6.3)	18 (6.2)
Nausea	23 (4.6)	15 (5.1)
Vomiting	6 (1.2)	8 (2.7)

- Current AEs significantly decreased patient HRQOL across all subscale and summary scale scores (all p<0.05) with the exception of cognitive function and mental health which did not show significant changes for all severity levels (Figure 1).
- AE severity resulted in larger reductions in HRQOL across all subscale and summary scores with the exception of cognitive function.
- AEs were more strongly associated with physical aspects of HRQOL compared to mental aspects, regardless of AE severity.

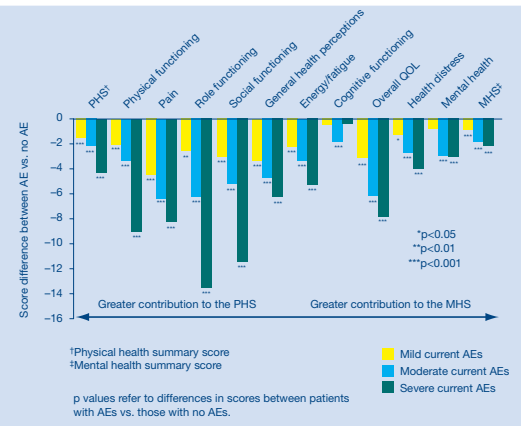

Figure 1: Current AEs and MOS-HIV scales

- Between group differences for both summary and all subscale scores favored TPV/r over CPI/r at Week 48 (Figure 2).
- Results were statistically significant for the MHS summary score (+1.47 points) and the energy/fatigue (+2.43 points), health distress (+2.93 points), general health perceptions (+3.53 points), mental health (+2.78 points) and overall QOL (+2.72 points) subscale scores (all p<0.05).

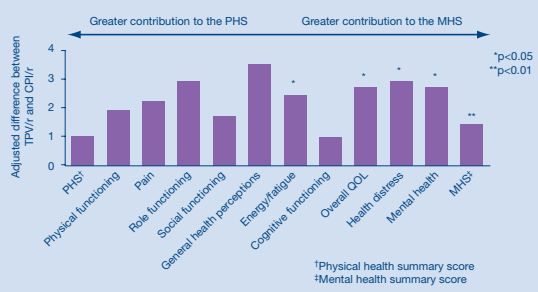

Figure 2: Difference in MOS-HIV scale and summary scores between TPV/r and CPI/r treatment groups at 48 weeks

Conclusions

- Exposure adjusted AEs in patients included in the HRQOL analysis were similar in the TPV/r and CPI/r treatment arms. Rates of any AE were higher in CPI/r patients while rates of drug-related AEs were higher in TPV/r patients.
- As expected, when AEs were present, the patient's HRQOL decreased. The impact on HRQOL was related to the severity of the AEs.
- Despite a higher incidence of treatment-related AEs, the overall HRQOL in TPV/r patients was stable or improved in comparison to the HRQOL of patients treated with CPI/r.

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