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Tipranavir/Ritonavir (TPV/r) Demonstrates Superior Immunologic Response to Comparator Protease Inhibitors (CPIs) in a PI-Experienced Population With Advanced Disease

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ABSTRACT

OBJECTIVES

Even modest improvements in the immunologic status of patients with CD4+ <200 cells/mm^3 have been shown to have a significant impact on clinical outcomes, reducing the incidence of AIDS-defining events and death. The phase 3, prospective, multicenter, randomized, open-label RESIST studies allowed for investigation of the immunologic response to TPV in PI-experienced patients with advanced disease.

METHODS

Patients with ≥3-class antiretroviral experience including ≥2 PI-based regimens; ≥1 primary PI mutation and ≤2 mutations at amino acids 33, 82, 84, 90; and viral load ≥1000 copies/mL and any CD4+ count were eligible. Before randomization, an optimized CPI/r-based regimen was selected; the selected PI could be new or continued from the current regimen.

RESULTS

1483 patients with a median baseline viral load of 4.8 $\log_{10}$ copies/mL, and median CD4+ cell count of 162 cells/mm^3 were treated. Preselected CPIs were lopinavir (LPV; 50%), amprenavir (APV; 26%), saquinavir (SQV; 20%), or indinavir (4%). Median CD4+ change was +34 cells/mm^3 with TPV/r and +4 cells/mm^3 with CPI/r (P<0.0001). When stratified by preselected CPI, increases in CD4+ were significantly greater with TPV/r than with LPV/r (+31 cells/mm^3 vs +6 cells/mm^3; P<0.0012), SQV/r (+36 cells/mm^3 vs +11 cells/mm^3; P<0.005), and APV/r (+30 cells/mm^3 vs +0 cells/mm^3; P<0.0001). A subgroup of patients (n=285) with very advanced disease (median baseline CD4+ cell count 72 cells/mm^3 in the TPV/r arm, and 77 cells/mm^3 in the CPI/r arm) included ENF in their background regimen. These patients experienced a change in CD4+ cell count of +55 cells/mm^3 (P<0.0001) with TPV +6 cells/mm^3 with CPI (P=0.3765). TPV also had a superior response to CPI in patients without ENF (+27 cells/mm^3 vs +3 cells/mm^3).

CONCLUSIONS

TPV provides a significantly greater CD4+ response than CPI in PI-experienced patients. In patients with very advanced disease, combination of TPV with ENF, an additional active background medication, provides a robust immunological response.

INTRODUCTION

Tipranavir (TPV) is a non-peptidic protease inhibitor (NPPI) recently approved by the US Food and Drug Administration. The companion phase 3 RESIST-1 and RESIST-2 trials demonstrated that TPV/r was superior to a standard-of-care boosted PI at 24 weeks.[1,2] TPV retains broad and potent in vitro antiviral activity against a wide range of patient-derived HIV isolates resistant to peptidic PIs.[3,4] Furthermore, TPV-based therapy produces potent, durable, and tolerable therapy in treatment-naive and PI-experienced HIV-1–infected patients.[5,6] In a 4-year follow-up study of treatment-experienced patients, TPV/r therapy was generally well-tolerated and adverse events were not associated with treatment discontinuation.[7] The trials were designed to allow combination of data from RESIST-1 and RESIST-2.

The planned analyses presented here compare the effects of TPV/r and CPI/r (LPV/r, SQV/r, and APV/r) on immunologic response. These analyses include the effect of other active antiretrovirals, including enfuvirtide (ENF), in the background regimen.

METHODS

The RESIST studies were phase 3, multicenter, open-label, randomized, comparative efficacy and safety studies of TPV/r 500 mg/200 mg twice daily compared with a genotypically defined, standard-of-care CPI/r (LPV/r, APV/r, SQV/r, or IDV/r). IDV/r was not included in the analysis since it was used by less than 4% of the patients. At randomization, patients were stratified according to a pre-selected PI and ENF use. Treatment response was defined as a confirmed ≥1 $\log_{10}$ decrease in viral load from baseline.

Patients were HIV+, triple-class, 2-PI–experienced males and females who satisfied the following criteria:

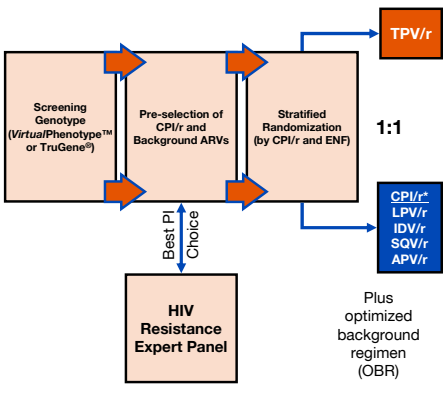
- ≥18 years old
- ≥3 consecutive months' experience with all 3 classes of ARVs
- ≥2 PI-based regimens for at least 3 months, 1 of which was the current treatment regimen
- Any CD4+ cell count was permissible
- Viral load of ≥1000 copies/mL
- ≥1 primary protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M
- ≤2 mutations at codons 33, 82, 84, 90 (key resistance mutations)

Key Exclusion Criteria

- All screening safety labs of DAIDS Grade 1 or greater
- Any recent drug holiday (7+ days in past 3 months)
- Use of investigational drugs or immunomodulatory drugs within 30 days of study entry
- Likely survival <12 months (investigator opinion, no Karnofsky score used)

RESIST STUDY DESIGN

Figure 1. Screening and Randomization



*CPI=comparator PI.

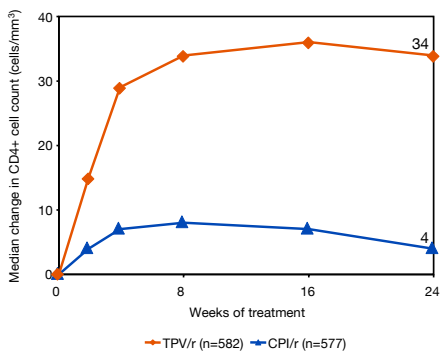
BASELINE DEMOGRAPHICS

Table 1. RESIST Patient Demographics

	Total (N=1159)	
	TPV/r	CPI/r
Total treated	582	577
Median age (years)	43	43
Percentage male	86.4	89.4
Race, white (%)	73.9	71.8
Median HIV-1 RNA ($\log_{10}$ copies/mL)	4.83	4.82
Median CD4+ cell count (cells/mm^3)	155	158
PI strata (%)		
LPV	50.3	50.3
SQV	20.1	20.5
APV	25.9	25.8
Total ENF use (%)	27.1	22.2
Median CD4+ cell count (cells/mm^3)	72	77

RESULTS: OVERALL IMPROVEMENT IN MEDIAN CD4+ CELL COUNT

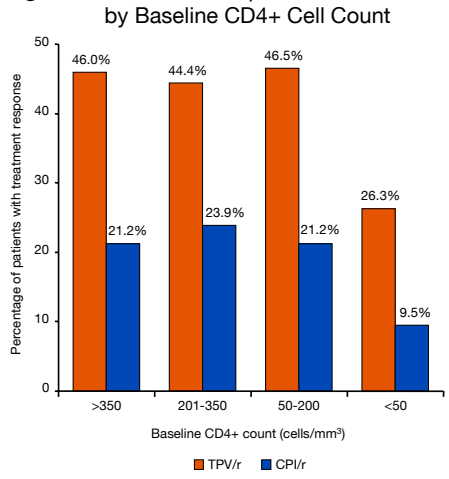
Figure 2. Median Change From Baseline in CD4+ Cell Count



- TPV/r showed a significantly higher increase in CD4+ cell counts compared with CPI/r (P<0.0001)

RESULTS: TREATMENT RESPONSE BY CD4+ CELL COUNT STRATA

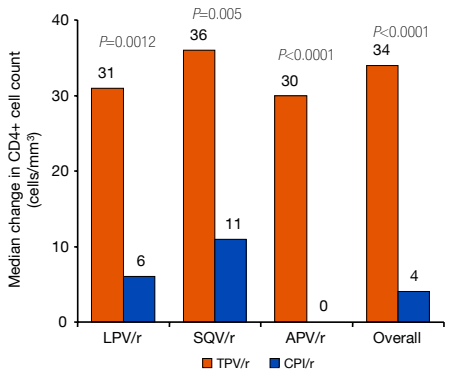
Figure 3. Treatment Response at Week 24 by Baseline CD4+ Cell Count



- Patients taking TPV/r had a higher treatment response than CPI/r arm regardless of baseline CD4+ (difference of 16.8% to 25.3%)
- Even in patients with a very low baseline CD4+ cell count (<50 cells/mm^3), a larger percentage of TPV/r recipients had a treatment response at week 24 than CPI/r recipients (26.3% vs 9.5%, respectively)

RESULTS: COMPARISON OF IMMUNOLOGIC RESPONSE WITH TPV/r AND LPV/R, SQV/r AND APV/r

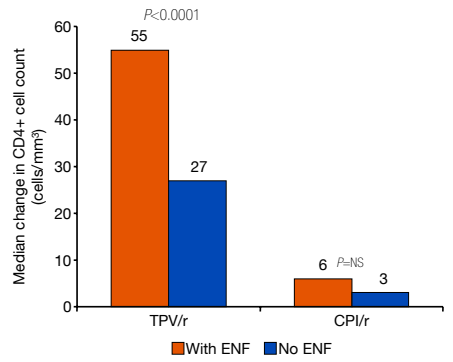
Figure 4. TPV/r Recipients Achieve a Greater Median Increase in CD4+ Cell Count at Week 24 Compared With CPI/r Patients



- Patients taking TPV/r had at least a 3-fold increase in median CD4+ cell count compared with each of the CPI/r arms and the CPI/r arms combined

RESULTS: IMPACT OF ENF IN OBR

Figure 5. ENF Recipients Achieve a Larger Increase in CD4+ Cell Count at Week 24 in the TPV/r Arm but Not in the CPI/r Arm



- Patients in the TPV/r arm had a significantly superior immunologic response as compared with patients in the CPI/r arm with and without ENF (P<0.0001)
- Patients taking TPV/r with ENF had a 9-fold larger increase in CD4+ cell count compared with those taking CPI/r with ENF (55 cells/mm^3 vs 6 cells/mm^3, P<0.0001)
  - Patients taking ENF had a lower median baseline CD4+ cell count than those not taking ENF (75 cells/mm^3 vs 180 cells/mm^3)
- CPI/r patients taking ENF had a median increase of 6 cells/mm^3, while CPI/r patients not taking ENF had a median increase of 3 cells/mm^3 (P=0.3765)

SUMMARY

- TPV/r demonstrated superior treatment response vs CPI/r in patients with both low and high CD4+ cell counts
- TPV/r use resulted in significantly larger increases in CD4+ cell counts compared with LPV/r, SQV/r, APV/r over 24 weeks
  - TPV/r was superior to LPV/r, SQV/r, and APV/r in all comparisons across a range of endpoints (see also Poster WePe6.3C07 presented at this conference)[8]
- In patients with AIDS (low CD4+ cell count), the addition of ENF enhanced the increase in CD4+ cell counts in patients receiving TPV/r, but not in those receiving CPI/r

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