

Correlation of Viral Load Reduction and Plasma Levels in Multiple Protease Inhibitor (PI)-Experienced Patients Taking Tipranavir/Ritonavir (TPV/r) in a Phase IIB Trial: BI 1182.52

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ABSTRACT

BACKGROUND

Tipranavir (TPV)-based therapy has demonstrated a uniquely robust resistance profile with sustained viral load response for up to 48 weeks of treatment in single and multiple PI-experienced patients. The preliminary target median plasma concentration for TPV has been set at 10X the protein-adjusted IC_{50} in multiple PI-resistant HIV-1. The study presented here, conducted in highly treatment-experienced patients, allows for further characterization of the plasma concentration profile of this novel nonpeptidic protease inhibitor (NPI).

METHODS

BI 1182.52 was a multicenter, international, randomized, blinded trial of three doses of TPV/r (500 mg/100 mg, 500 mg/200 mg, and 750 mg/200 mg). Plasma concentrations of TPV were measured 8 to 16 hours following the last drug administration on days 7 and 14.

RESULTS

Two hundred sixteen patients with a median baseline viral load of 4.5 \log_{10} copies/mL and CD4+ cell count of 153 cells/mm³ were randomized and received treatment. The median trough plasma concentrations of TPV exceeded the target value in all arms. TPV/r plasma concentrations on days 7 and 14 were 21.8 μ M and 20.1 μ M, 32.1 μ M and 29.1 μ M, and 52.2 μ M and 42.6 μ M for the 500/100, 500/200, and 750/200 doses, respectively. 78% and 77% of patients in the 500/200 and 750/200 arms, respectively, achieved the target plasma concentration, compared with 48% in the 500/100 arm. There was greater variability of plasma levels in the 750/200 arm. The median change in viral load for patients with TPV C_{min} s of ≤ 2 , 2 to 5, 5 to 10, 10 to 15, 15 to 20, and >20 μ M was -0.32 \log_{10} , -0.62 \log_{10} , -1.11 \log_{10} , -0.40 \log_{10} , -1.14 \log_{10} , and -1.10 \log_{10} , respectively.

CONCLUSIONS

The consistency of trough plasma levels from days 7 to 14 indicates that steady state is reached within the first 7 days of treatment in these highly treatment-experienced patients (switched from PI). These results indicate that a consistently robust viral load response was achieved in patients with trough plasma concentrations >15 μ M; more patients in the 500/200 and 750/200 arms of the study achieved this concentration than in the 500/100 arm. All doses of TPV/r studied achieved the preliminary target plasma levels, reaching a median plasma concentration well in excess of 10X the IC_{50} for PI-resistant virus.

INTRODUCTION

Tipranavir (TPV) is a nonpeptidic protease inhibitor (NPI) that has demonstrated a uniquely robust resistance profile against a large panel of isolates resistant to available peptidic PIs.¹ Furthermore, in Phase II studies of single and multiple PI-experienced patients, a minimum of 16 to 20 protease gene mutations was required for reduced susceptibility to TPV.^{2,3} Sustained viral load response was demonstrated for up to 48 weeks of treatment in these studies. Larder et al attributed this to the greater conformational flexibility afforded TPV by its predominantly hydrophobic interactions with the protease enzyme, compared with PIs that interact mainly via hydrogen bonds. As a result, TPV may provide an important therapeutic option for treatment-experienced patients.

TPV is dosed in combination with low-dose ritonavir to attain therapeutically relevant plasma concentrations (>10 X protein adjusted IC_{50} for PI-resistant HIV-1) with twice-daily dosing. The objective of this trial was to determine the final dose for Phase III trials based on the virologic response after 14 days of functional monotherapy, and safety assessment after 4 weeks of treatment, as well as pharmacokinetic (PK) assessments. Doses of TPV were chosen for this trial if they had demonstrated good virologic suppression, acceptable toxicity, and had reached median TPV trough plasma levels 10X IC_{50} for resistant virus.⁴ Phase III trials of TPV will be conducted in highly treatment-experienced patients, randomized to receive TPV/r or a ritonavir-boosted PI plus optimized background therapy. The final dose of TPV/r for study in Phase III trials will be determined based on this trial.

METHODS

STUDY DESIGN:

- Double-blinded, randomized trial using three doses of TPV/r
- At entry, patients replaced their original PI with one of three TPV/r dose regimens:
 - TPV/r 500 mg/100 mg twice daily (500/100)
 - TPV/r 500 mg/200 mg twice daily (500/200)
 - TPV/r 750 mg/200 mg twice daily (750/200)

- During the 14-day trial, all patients remained on NRTI(s) and/or NNRTI(s) from their failing regimen. After 2 weeks of functional monotherapy, background antiretroviral medications were optimized based on the results of genotypic resistance testing

ENTRY CRITERIA:

- Patients with multiple-PI experience and virologic failure on a current PI-based regimen
- > 3 months NRTI and NNRTI treatment experience
- HIV-1 RNA >1000 copies/mL, any CD4+ cell count
- Visible Genetics TruGene[®] genotypic resistance report indicating at least one primary PI resistance mutation from among 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, and 90M, with not more than one among 82L/T, 84V, or 90M

ANALYSIS:

- Morning trough plasma concentrations (C_{min}) of TPV were measured 8 to 16 hours following the last drug administration on days 7 and 14

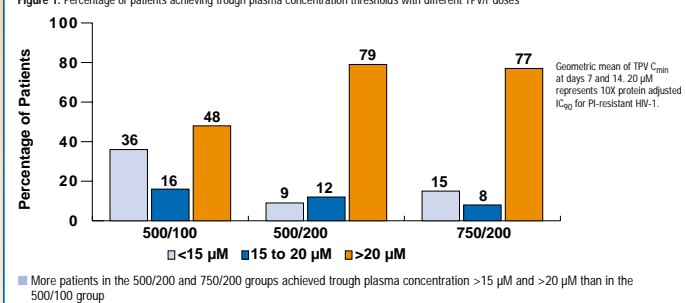
Baseline characteristics

Table 1. Demographics and baseline characteristics

	Number (%) of patients			
	500/100 (n = 73)	500/200 (n = 72)	750/200 (n = 71)	Total (N = 216)
Age (years)				
Median (%)	43	42.5	42	42
Range	29-68	28-63	30-64	28-68
Gender (%)				
Male (%)	63 (86.3)	60 (83.3)	59 (83.1)	182 (84.3)
Female (%)	10 (13.7)	12 (16.7)	12 (16.9)	34 (15.7)
Race (%)				
White	56 (76.7)	56 (77.8)	53 (74.6)	165 (76.4)
Black	17 (23.3)	16 (22.2)	17 (23.9)	50 (23.1)
Asian	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)
Baseline CD4+ cell count (cells/mm ³)				
Median	140	162	133	153
Range	2-773	1-476	1-712	1-773
Baseline HIV RNA (\log_{10} copies/mL)				
Median	4.49	4.57	4.53	4.53
Range	2.61-6.43	2.85-5.99	2.89-6.25	2.61-6.43
Hepatitis coinfection				
Hep B (SAg+)	2 (2.7)	4 (5.6)	6 (8.5)	12 (5.6)
Hep C (HCV RNA+)	9 (12.3)	6 (8.3)	7 (9.9)	22 (10.2)
Hep B and Hep C	0 (0.0)	0 (0.0)	2 (2.8)	2 (0.9)

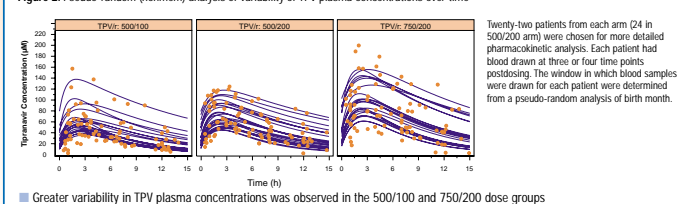
Comparison of pharmacokinetics of TPV/r doses

Figure 1. Percentage of patients achieving trough plasma concentration thresholds with different TPV/r doses



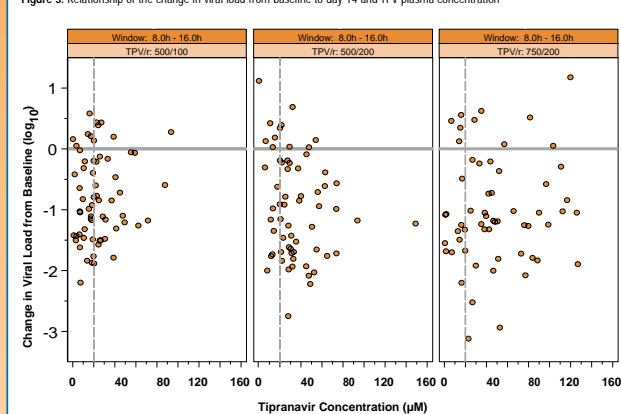
Population pharmacokinetic analysis of TPV plasma concentrations

Figure 2. Pseudo-random (nonmem) analysis of variability of TPV plasma concentrations over time



Effect of TPV plasma concentrations on viral load response

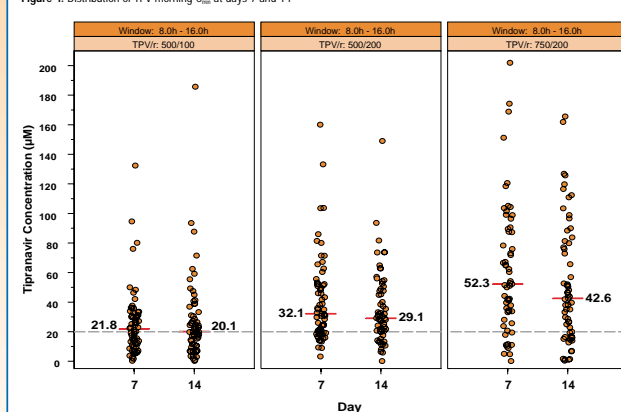
Figure 3. Relationship of the change in viral load from baseline to day 14 and TPV plasma concentration



Each circle represents an individual patient. The strength of the efficacy/PK relationship is determined by the number of patients in the lower right quadrant of each chart. No change in viral load is represented by the solid horizontal line at 0. The broken vertical line at 20 μ M indicates 10X TPV IC_{50} for PI-resistant HIV-1.
At $C_{min} >20$ μ M the median change in viral load was -0.79 \log_{10} in the 500/100 group, compared with -1.16 \log_{10} and -1.11 \log_{10} in the 500/200 and 750/200 groups, respectively

TPV trough plasma concentrations

Figure 4. Distribution of TPV morning C_{min} at days 7 and 14



Individual TPV trough plasma concentrations for patients enrolled in each arm are represented by the circles. The median trough concentrations are represented by the horizontal red bars. The broken line at 20 μ M indicates 10X TPV IC_{50} for PI-resistant HIV-1.

- Steady state was reached by day 7
- TPV trough concentrations increased with increased TPV/r dose

Viral load response at different TPV C_{min} thresholds

Table 2. Median change from baseline in viral load at 2 weeks according to TPV trough plasma levels* by treatment group

TPV C_{min} (μ M)	n	Change in viral load	500/200	n	Change in viral load	750/200	n	Change in viral load	Total	n	Change in viral load
<2	1	-0.32	1	1.12	1	-1.55	3	-0.32			
2-5	4	-0.62	1	-0.30	1	-1.62	6	-0.62			
5-10	7	-1.11	2	-0.94	2	-1.39	11	-1.11			
10-15	13	-0.98	2	0.21	6	-0.04	21	-0.40			
15-20	11	-1.11	8	-0.40	5	-1.67	24	-1.13			
>20	33	-0.85	51	-1.15	49	-1.19	133	-1.10			
Total patients	69		65		64		198				

*Intra-individual geometric mean TPV trough plasma levels at days 7 and 14.
A less consistent reduction in viral load was noted when TPV C_{min} was below 15 μ M

SUMMARY

- Median morning $C_{min} >10$ X IC_{50} for PI-resistant HIV-1 was achieved for all dose groups
- 79% and 77% of patients in the 500/200 and 750/200 dose groups, respectively, achieved morning $C_{min} >20$ μ M
- The least interpatient variability in TPV plasma concentrations was seen with the 500/200 dose
- Steady state was reached by day 7
- All doses were generally well tolerated*
- 500/100 dose was eliminated from further consideration due to lower plasma levels and reduced activity in patients with ≥ 20 PI mutations at baseline*
- 500/200 dose selected for Phase III RESIST program

*See also abstracts 179 and 596 for efficacy/safety and resistance results from BI 1182.52.

CONCLUSIONS

In combination with efficacy and safety data from this trial (see abstracts 179 and 596), the 500/200 dose of TPV/r was chosen to be taken forward into Phase III trials.^{5,6} Although all doses demonstrated similar virologic efficacy across this study population, lower plasma concentrations were associated with an inconsistent virologic response. As a result, the lower overall plasma levels observed in the 500/100 group raise concerns for this dose's activity in patients with high-level PI resistance in light of emerging analyses of viral load response by baseline drug susceptibility and genotype. The 500/200 dose has consistently produced TPV trough plasma levels in excess of 10X the IC_{50} for PI-resistant HIV-1. The higher 750/200 dose demonstrated a similar proportion of patients with TPV trough plasma levels above 20 μ M, but with greater variability. This variability may be related to lower treatment compliance associated with an observed increase in the incidence of adverse events in this group. The efficacy and safety of TPV/r 500/200 is presently being investigated in the ongoing Phase III RESIST program.

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