Efficacy and safety of two doses of tipranavir/ritonavir versus lopinavir/ritonavir-based therapy in antiretroviral-naïve patients: results of BI 1182.33

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Abstract

Purpose of the Study Tipranavir (TPV) is a PI with potent activity against multi-PI resistant HIV-1. TPV/r 500/200 mg bid provides superior efficacy to other PI/r in highly treatment-experienced (HTE) patients. We compared safety and efficacy of two TPV/r doses with lopinavir/ritonavir (LPV/r) in antiretroviral (ARV)-naïve patients.

Methods A dose ranging, multicentre, open-label trial randomised 562 ARV-naïve patients to 3TC/tenofovir + TPV/r 500/100 mg bid (TPV/r-100), 500/200 mg bid (TPV/r-200) or LPV/r 400/100 mg bid (LPV). Primary endpoint was confirmed viral load (VL) <50 copies/mL at Week 48 without prior ARV changes.

Summary of Results Baseline (BL) characteristics were similar. At Week 48, similar %s had confirmed VL <50 copies/mL: 65.8% (TPV/r-100), 66.7% (TPV/r-200), 69.2% (LPV) (ITT); 80.1%, 81.4%, 83.0% (OT). No differences in responses were detected regardless of BL VL. Median CD4 cell counts increased in all arms (+172, +175, +207 cells/mm^3). Higher % of patients in TPV/r-200 arm had Grade 3/4 (G3/4) ALT elevations (19.6%) vs. TPV/r-100 (6.0%) and LPV/r arms (3.8%). G3/4 triglyceride rates were similar in all arms.

Conclusions The TPV/r-200 arm was closed due to higher rate of G3/4 ALT elevations. While non-inferiority was achieved with data collected up to Week 48 in all arms, TPV/r-100 was no longer non-inferior using Week 60 data from all patients due to a higher discontinuation rate based on a less favourable GI tolerability profile.

Introduction

Tipranavir (TPV) is a new generation protease inhibitor (PI) with potent activity against multi-PI resistant HIV-1 [1]. In combination with an optimised background regimen, TPV co-administered with low dose ritonavir (TPV/r) at a dose of 500/200 mg BID provided superior efficacy to comparator PI/r in highly treatment experienced (HTE) patients for at least 96 weeks [2,3].

We compared the safety and efficacy of two TPV/r doses with a standard dose of lopinavir/ritonavir (LPV/r) in antiretroviral (ARV)-naïve patients (study BI1182.33). All patients also took lamivudine (3TC) and tenofovir.

Patients

BI1182.33 was a dose ranging, multi-centre, open-label trial (Figure 1). Patients were HIV-infected, ARV naïve adults (≥18 years old) with a baseline VL ≥5,000 copies/mL and a CD4 cell count <500 cells/mm^3 . There were no entry restrictions with respect to very low CD4 counts. A total of 562 ARV-naïve patients were randomised to receive 3TC/tenofovir + TPV/r 500/100 mg bid (TPV/r-100), 500/200 mg bid (TPV/r-200) or LPV/r 400/100 mg bid (LPV), stratified according to CD4 cell counts of <200 or ≥200 cells/mL.

Study design

The study design of BI 1182.33 is shown in Figure 1.

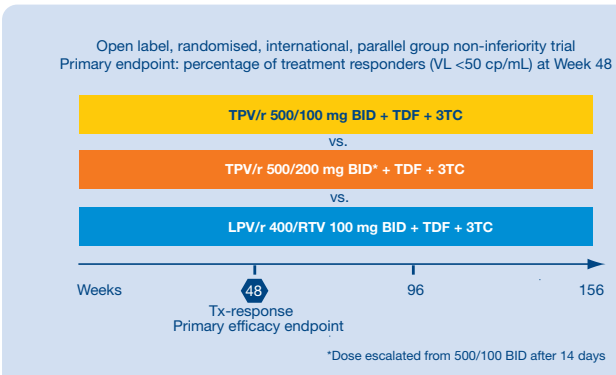

Figure 1: Design of BI 1182.33 study

The primary endpoint was a confirmed viral load (VL) <50 copies/mL at Week 48 without prior antiretroviral (ARV) changes.

Non-inferiority between each TPV/r group and the LPV/r group was concluded if the lower limit of the 97.5% confidence interval for the difference in response rate, adjusted for CD4 stratum, was not less than or equal to the pre-defined non-inferiority margin of 15%.

Results

Patients

Table 1 summarises the baseline characteristics of patients enrolled in BI1182.33 (Full Analysis Set [FAS]). Approximately one quarter of the patients (23.5%) were female. The median CD4 cell count was 207 cells/mm^3 and the median VL was 5.03 $\log_{10}$ copies/mL.

Table 1: Baseline characteristics of patients enrolled in BI1182.33 (FAS)

	TPV/r-100	TPV/r-200	LPV/r	Total
Total treated	187	186	185	558
Male (N [%])	137 (73.3)	146 (78.5)	144 (77.8)	427 (76.5)
Female (N [%])	50 (26.7)	40 (21.5)	41 (22.1)	131 (23.5)
White (N [%])	141 (75.4)	134 (72.0)	134 (72.4)	409 (73.3)
Median age (years)	35	36	35	35
Median VL	4.98	5.05	5.06	5.03
VL >100,000 copies/mL (N [%])	85 (45.5%)	97 (52.2%)	93 (50.3%)	275 (49.3%)
Median CD4	216.0	197.0	208.0	206.8
CD4 <50 cells/mm^3 (N [%])	18 (9.6%)	24 (12.9%)	21 (11.4%)	63 (11.3)
Hepatitis co-infected (N [%])	30 (16.0%)	33 (17.7%)	28 (15.1%)	91 (16.3%)

Figure 2 depicts the disposition of patients at Week 48.

Virological efficacy

At Week 48, similar proportions of patients in each study arm had confirmed VLs <50 copies/mL (Intent to Treat analysis [ITT]) (Figure 3):

- TPV/r-100: 65.8%
- TPV/r-200: 66.7%
- LPV/r: 69.2%

The primary analysis comparing treatment response among treatment groups showed non-inferiority (CD4 stratum adjusted 97.5 C.I.s (–14.2, 7.1) and (–11.8, 9.6) for TPV/r-100 and TPV/r-200 compared to LPV/r, respectively).

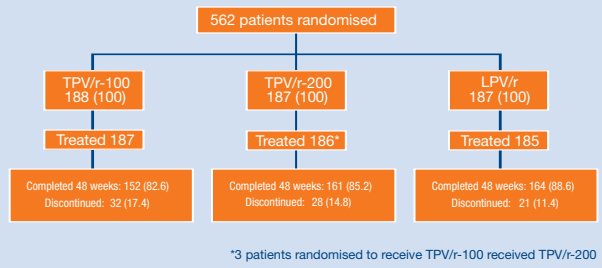

Figure 2: Disposition of patients at Week 48

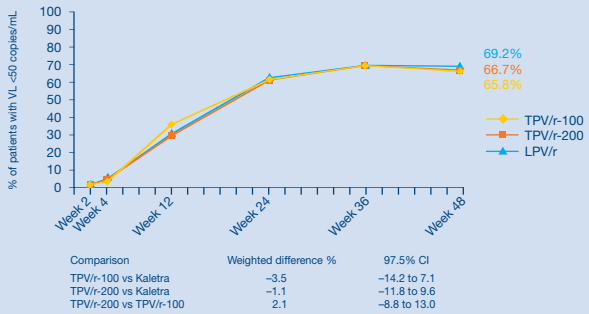

Figure 3: Week 48 virological response: proportions of patients with confirmed VL <50 copies/mL

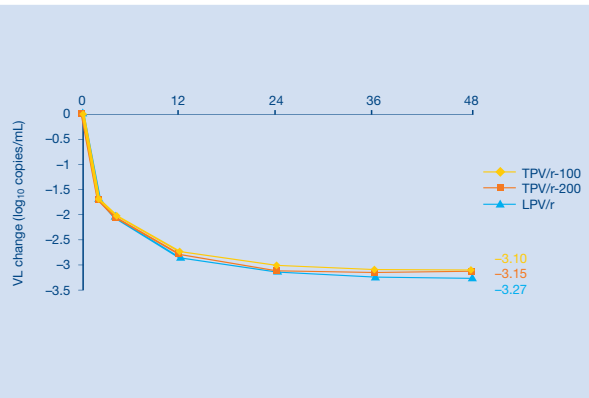

Figure 4: Median change in VL over 48 weeks (LOCF analysis)

Since treatment response was defined as a confirmed VL <50 copies/mL and some patients achieved their first VL <50 copies/mL at Week 48, a post-hoc Week 48 analysis was conducted. Since Week 60 was the visit immediately following Week 48, the Week 48 post-hoc analysis included data up until Week 60 in all patients in order to allow VL confirmation to patients who had their first VL <50 copies/mL at Week 48. When Week 60 data were included for all patients in this post-hoc analysis, the lower limit of the 97.5% confidence interval for TPV/r-100 – LPV/r (–15.03, 5.8) extended below the pre-defined non-inferiority margin of 15% resulting in TPV/r-100 no longer being demonstrated to be non-inferior to LPV/r.

The median change in VL over 48 weeks (last observation carried forward [LOCF] analysis), shown in Figure 4, was comparable between treatment groups.

Immunological efficacy

Median CD4 cell counts increased in all arms by Week 48: +172, +175, +207 cells/mm^3 in the TPV/r-100, TPV/r-200 and LPV arms, respectively, (LOCF analysis) (Figure 5).

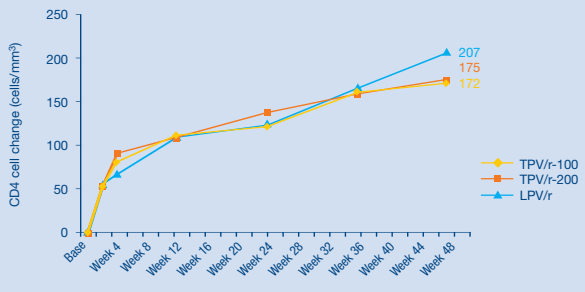

Figure 5: Median change in CD4 cell counts over 48 weeks (OT analysis)

Safety

Table 2 provides an overall summary of adverse events reported by Week 48.

A higher proportion of patients in the TPV/r-200 arm had Grade 3/4 ALT elevations (17.7%) than in the TPV/r-100 (5.9%) or LPV/r arms (3.4%) (Figure 6). Despite this increased rate, no clinical cases of hepatitis or hepatic failure or fatal cases due to hepatotoxicity occurred in the TPV/r-200 arm.

Triglyceride and cholesterol elevations, stratified by Grade, over 48 weeks are depicted in Figure 7. The low rates of Grade 3/4 elevations in triglyceride and lipid levels were similar in all three study arms.

Table 2: Adverse events – overall summary at Week 48

	TPV/r-100 N (%)	TPV/r-200 N (%)	LPV/r N (%)
Number of patients	184 (100)	189 (100)	185 (100)
Patients with any AE	160 (87.0)	172 (91.0)	164 (88.6)
Patients with investigator-defined drug-related AEs	115 (62.5)	131 (69.3)	102 (55.1)
Patients with serious AEs	25 (13.6)	23 (12.2)	11 (5.9)
Total with any study drug-related serious AEs	2 (1.1)	2 (1.1)	2 (1.1)

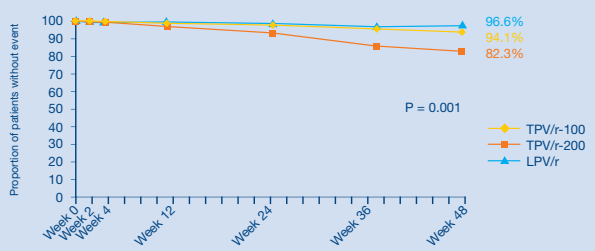

Figure 6: Grade 3–4 ALT elevations over 48 weeks (proportion of patients with an event)

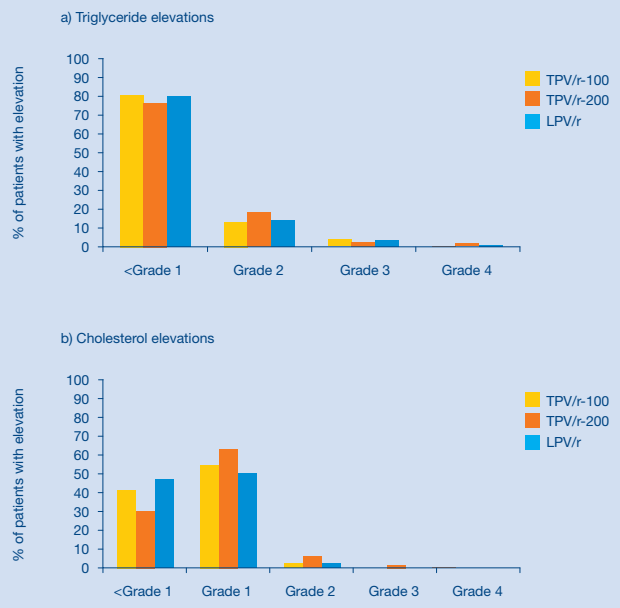

Figure 7: Triglyceride and cholesterol elevations over 48 weeks, stratified by Grade

Conclusions

- The results of a post-hoc Week 48 efficacy analysis performed after all patients had completed a Week 60 visit (when they could have confirmed a first VL <50 copies/mL at Week 48) showed that the 500/200 mg BID dose of TPV/r was non-inferior to LPV/r. However, the 500/100 mg BID dose of TPV/r could no longer be considered non-inferior.
- The two TPV/r doses tested were effective in treatment-naïve patients:
  - Similar proportions of patients achieved a VL <50 copies/mL at Week 48 in both arms.
  - Similar increases in CD4 cell counts in both arms.
- There was a higher rate of patients who experienced Grade 3/4 ALT elevations in patients receiving TPV/r 500/200 mg BID compared with those taking LPV/r or TPV/r 500/100 mg BID.
- The proportions of patients experiencing Grade 3/4 lipid elevations were comparable among arms.
- At the doses tested in this trial, TPV/r cannot be recommended for ARV-naïve patients infected with wild type HIV-1.

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