P7.2/04

Safety and tolerability of darunavir/ritonavir in treatment-experienced HIV-1-infected patients at 96 weeks in the POWER 1, 2 and 3 trials

Yeni P,[1] Roberts A,[2] Van Baelen B,[3] Lavreys L[3]

[1]Hôpital Bichat and University of Paris, Paris, France; [2]George Washington University Medical Center, Washington, DC, USA; [3]Tibotec BVBA, Mechelen, Belgium

Address correspondence to: P Yeni, MD, Service des Maladies Infectieuses, Hôpital Bichat, 75877 Paris CEDEX 18, France; Fax: +33 140 256 774; E-mail: patrick.yeni@bch.ap-hop-paris.fr

Introduction

- The protease inhibitor (PI) darunavir (DRV; TMC114) with low-dose ritonavir (DRV/r) at a dose of 600/100mg bid has been approved in Europe,[1] the USA[2] and other countries for the treatment of HIV-1 infection in treatment-experienced adults.
- POWER 1 and 2 (TMC114-C213 and C202) are randomised, controlled, Phase IIb, 144-week trials designed to evaluate the efficacy and safety of DRV/r in comparison with currently available PIs (CPIs) in treatment-experienced patients, in combination with an optimised background regimen (OBR)
  – at both Weeks 24 and 48, patients receiving DRV/r 600/100mg bid had significantly greater virological and immunological responses than patients receiving CPIs;[3–5] 45% of DRV/r patients versus 10% of CPI patients achieved a viral load <50 copies/mL at 48 weeks[5]
  – DRV/r 600/100mg bid was generally well tolerated to Week 48, with incidences of adverse events (AEs) lower than or similar to those in patients receiving CPI(s).
- POWER 3 is an analysis of two open-label, non-randomised trials (TMC114-C215 and C208) evaluating the efficacy and safety of DRV/r 600/100mg bid plus an OBR in a larger set of treatment-experienced patients.[6] At Week 48, 45% of patients achieved a viral load <50 copies/mL and DRV/r was generally well tolerated, with a similar safety and tolerability profile to that observed in POWER 1 and 2.[7]
- These findings are supported by recent 48-week clinical data from Phase III trials, where lower incidences of gastrointestinal-related AEs were observed with DRV/r compared with ritonavir-boosted lopinavir (LPV/r).[8,9]
- This pre-planned combined analysis of POWER 1, 2 and 3 evaluated the longer-term safety and tolerability of DRV/r 600/100mg bid, when all patients had reached Week 96 or discontinued earlier.

Methods

Patients

- Patients were male or female, aged ≥18 years, with HIV-1 RNA >1,000 copies/mL and ≥1 primary PI mutation (based on the IAS-USA 2003 list[10] for POWER 1 and 2 and the IAS-USA 2004 list[11] for POWER 3) at screening.
- Patients had received a PI-containing regimen for at least 8 weeks prior to screening, and had previously used ≥1 NRTI for at least 3 months, ≥1 NNRTI and ≥1 PI for at least 3 months. Previous use of enfuvirtide was permitted.
- Hepatitis B or C co-infected patients were included in POWER 1 and 3 if they were clinically stable and would not require treatment, but such patients were excluded from POWER 2.
- Major exclusion criteria included acute hepatitis A at screening; any currently active AIDS-defining illness, use of a treatment interruption schedule at screening, previous randomisation to a DRV treatment arm, and use of investigational antiretroviral therapy at screening.
- The study protocols were reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study design

- In POWER 1 and 2, randomisation at baseline was to either DRV/r (400/100mg qd, 800/100mg qd, 400/100mg bid, or 600/100mg bid), or to one or more investigator-selected CPI(s) (excluding tipranavir [TPV], which was not commercially available at the time of study initiation). All patients also received an OBR (two or more NRTIs, with or without enfuvirtide), selected on the basis of screening genotypic resistance and treatment history.
- Following the 24-week dose-finding phase and primary efficacy analysis, all patients receiving lower doses of DRV/r in POWER 1 and 2 were switched to the 600/100mg bid dose
  – the 96-week safety analysis included 131 patients who had received DRV/r 600/100mg bid from baseline
  – analysis of 96-week safety data from patients in the CPI group was not conducted because of the reduction in sample size due to the high rate of discontinuation in this treatment arm (mostly as a result of virological failure).
- All 336 patients in POWER 3 received DRV/r 600/100mg bid with an OBR (selected as for patients in POWER 1 and 2) and were included with data from baseline.

Safety analyses

- Safety and tolerability were continuously monitored and reviewed throughout the trials by an independent data and safety monitoring board. All randomised and treated patients with baseline or post-baseline data, regardless of their eligibility or compliance with the protocol, were included in the analysis with data from baseline to the analysis cut-off date (intent-to-treat population).
- AEs and clinical laboratory evaluations were assessed at screening, baseline, weekly during the first month, biweekly during the second and third months, every 4 weeks until Week 24, every 8 weeks until Week 48 and every 12 weeks thereafter. Unscheduled visits undertaken to obtain additional safety data and follow-up assessments were also taken into account. The protocol specified that patients fasted for at least 8 hours before blood sampling for biochemistry tests.

Results

Patient disposition

- The analysis included 467 patients: 131 patients who had received DRV/r 600/100mg bid from baseline in POWER 1 (n=65) and POWER 2 (n=66), and 336 patients who initiated treatment with DRV/r 600/100mg bid in POWER 3. The demographics and baseline disease characteristics are shown in Table 1.

Table 1. Demographics and baseline disease characteristics for patients receiving DRV/r 600/100mg bid from baseline in POWER 1, 2 and 3.

Parameter	DRV/r 600/100mg bid (N=467)
Demographics	
Male, n (%)	409 (88)
Mean age, years (SD)	44.2 (7.87)
Caucasian, n (%)	355 (76)
Baseline disease characteristics	
Mean HIV infection duration, years (SD)	12.7 (4.29)
Mean viral load, $\log_{10}$ copies/mL (SD)	4.59 (0.76)
Median CD4 cell count, cells/mm^3 (range)	129 (0–831)
CDC category C, n (%)	233 (50)
Previous treatment experience	
Median duration previous NRTIs, months (range)	98 (2–238)
Median duration previous NNRTIs, months (range)	23 (1–164)
Median duration previous PIs, months (range)	71 (1–151)
Previous TPV use, n (%)	110 (24)
Previous enfuvirtide use, n (%)	133 (29)
Baseline genotype and phenotype	
Median number of primary PI mutations[12] (range)	4.0 (0–8)
Median number of PI resistance-associated mutations[12] (range)	12.0 (1–19)
Median DRV FC (range)	3.3 (0.1–503.2)

SD = standard deviation
FC = fold change in EC_{50}

- The mean duration of treatment was 90.5 weeks (SD 32.1). At the time of analysis, 149 patients (32%) had discontinued
  – the main reasons for discontinuation were virological failure (63 patients, 13%) and AEs (39 patients, 8%)
  – AEs leading to permanent treatment discontinuation reported as at least possibly related to DRV/r were reported in 1.7% of patients.

Adverse events

- In general, the safety and tolerability observations at Week 96 confirmed the findings at Week 48. DRV/r was not associated with any new safety concerns.
- The majority of the AEs reported were grade 1–2 in severity. Apart from enfuvirtide-associated injection site reaction (116 patients [25%]), the most common individual treatment-emergent AEs were diarrhoea, nausea, nasopharyngitis, and headache (Table 2).
- A total of 196 patients (42%) reported at least one grade 3 or 4 AE, of which most were considered unrelated or doubtfully related to DRV/r (53 [11%] were considered at least possibly related to DRV/r).

Table 2. Treatment-emergent AEs in POWER 1, 2 and 3.

Incidence, n (%)	DRV/r 600/100mg bid (N=467)
Any AE	455 (97)
AEs reported in ≥10% of patients, regardless of severity and causality	
Diarrhoea	118 (25)
Nasopharyngitis	75 (16)
Nausea	75 (16)
Headache	74 (16)
Bronchitis	63 (13)
Sinusitis	63 (13)
Cough	54 (12)
Herpes simplex	51 (11)
Fatigue	49 (10)
Arthralgia	49 (10)
Pyrexia	47 (10)
Rash (all types)*	47 (10)
AEs of grade 2–4 at least possibly related to DRV/r (≥2% of patients)‡	
Diarrhoea	16 (3)
Vomiting	12 (3)
Nausea	10 (2)
Headache	10 (2)

*All rash-related AEs were grade 1 or 2 in severity except for one case of grade 3 drug-related skin eruption, which led to permanent treatment discontinuation
‡Excluding laboratory abnormalities reported as AEs

- In general, little change in the type and incidence of AEs was observed over time and there were no cumulative toxicity effects with longer-term DRV/r treatment.
- Serious AEs (SAEs) were reported in 125 (27%) patients; the most commonly observed were pneumonia (2%), acute renal failure (1%), vomiting (1%) and pyrexia (1%). All other SAEs occurred in <1% of patients.
- Twenty patients (4%) died during the treatment period (n=2 in POWER 1, n=4 in POWER 2 and n=14 in POWER 3). All deaths were considered to be unrelated or doubtfully related to study medication. The overall mortality rate was 2.5 per 100 patient-years exposure and did not increase over time. The majority of deaths (15 [75%]) occurred in patients with baseline CD4 cell counts of <50 cells/mm^3, a factor known to be associated with a higher risk of mortality.

Laboratory parameters

- Changes in laboratory parameters between baseline and Week 96 confirmed the findings of previous analyses
  – mean changes from baseline in triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein (LDL) were –0.59 (standard error [SE] 0.15), 0.46 (SE 0.07), 0.08 (SE 0.02) and 0.53 (SE 0.06) mmol/L, respectively.
- Most laboratory abnormalities were grade 1 or 2 in severity. Treatment-emergent grade 2–4 laboratory abnormalities are shown in Table 3 (post-baseline laboratory data was available for 462 patients).

Table 3. Treatment-emergent grade 2–4 laboratory abnormalities observed in ≥2% of patients in POWER 1, 2 and 3.

Incidence, n (%)	DRV/r 600/100mg bid (N=462)
Increased total cholesterol	115 (25)
Increased LDL	103 (22)
Increased triglycerides	99 (21)
Hyperglycaemia	80 (17)
Increased pancreatic amylase	75 (16)
Decreased neutrophils	63 (13)
Increased AST	49 (11)
Increased ALT	43 (9)
Increased pancreatic lipase	40 (9)
Decreased white blood cell count	37 (8)
Increased partial thromboplastin time	36 (8)
Decreased platelet count	30 (6)
Increased creatinine	27 (6)
Increased ALP	22 (5)
Decreased haemoglobin	18 (4)
Increased prothrombin time	11 (2)
Hyperbilirubinaemia	10 (2)

AST = aspartate aminotransferase
ALT = alanine aminotransferase
ALP = alkaline phosphatase

Conclusions

- Treatment with DRV/r 600/100mg bid was generally well tolerated by treatment-experienced patients over 96 weeks, with no new safety concerns identified.
- The most frequently reported treatment-emergent AEs (regardless of severity and causality) were diarrhoea, nausea, nasopharyngitis and headache, each of which occurred in no more than 25% of patients.
- The majority of AEs were grade 1 or 2 in severity. Discontinuation due to AEs was infrequent.
- Results of the clinical laboratory evaluations confirmed those of the previous analyses. Most graded laboratory abnormalities were grade 1 or 2 in severity.
- The results of this analysis confirm and extend the safety and tolerability findings at Weeks 24 and 48. The safety findings for DRV/r from the POWER trials are also confirmed by the results of Phase III studies, where DRV/r treatment was generally well tolerated in treatment-experienced (600/100mg bid)[8] and treatment-naïve (800/100mg qd)[9] patients.

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Supported by Tibotec

Presented at the 11th European AIDS Conference, Madrid, Spain, 24–27 October 2007.

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