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Relative antiviral efficacy of TMC114/r and tipranavir/r versus control PI in the POWER and RESIST trials

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Abstract

Aim: To compare the relative antiviral efficacy of TMC114 with low-dose ritonavir (TMC114/r) and tipranavir (TPV/r) versus control protease inhibitor (PI) in treatment-experienced patients, using data from POWER 1 and 2 and RESIST 1 and 2 trials. The four trials all recruited antiretroviral (ARV) experienced patients with HIV RNA >1,000 and at least one primary PI mutation, used optimised NRTIs with or without enfuvirtide (ENF), plus investigator-selected control PI (CPI) in the control arms, and had the same primary efficacy endpoint.

Methods: Summary statistics were obtained from published presentations and drug labels. For the POWER trials, data from the 600/100mg bid dose and CPI arms was included, while all data from the RESIST trials (TPV/r 500/200mg bid and CPI) were included. The difference in Week 24 efficacy for the new PI versus CPI were compared between the trials. All analyses were using intent-to-treat (ITT) time to loss of virological response (TLOVR) methods.

Results: Overall baseline characteristics (age, gender, race, HIV RNA, IAS-USA PI mutations) were well matched across the trials. At Week 24, 71% of TMC114/r patients achieved a ≥1 $\log_{10}$ reduction in HIV RNA compared with 40% of TPV/r patients (CPI patients 21% and 18%, respectively). The treatment benefit of TMC114/r over CPI in the POWER trials was greater (outside the 95% confidence intervals [CIs]) than the benefit of TPV/r over CPI in the RESIST trials, for the 24-week HIV RNA endpoints of ≥1 log reduction, <400 copies and <50 copies/mL, plus for mean rise in CD4 count. This effect was also found for the subgroups of ENF-naïve patients and patients not using ENF.

Conclusions: Given the caveats of cross-study analysis, the efficacy benefits of TMC114/r versus CPI in the POWER trials appear to be greater than the benefits of TPV/r versus CPI in the RESIST trials, for HIV RNA suppression and CD4 rises.

Introduction

- TPV and TMC114 are novel PIs with clinical activity against HIV strains resistant to other approved PIs.[1,2] Both TPV and TMC114 are boosted with ritonavir to achieve higher and more stable plasma PI concentrations.
- TPV/r is given at a dose of 500/200mg bid,[3] while TMC114/r is given at a dose of 600/100mg bid.[2] Both PIs have been evaluated in clinical trials and compared with conventional PI treatment – the RESIST 1 and 2 trials for TPV/r,[1] and the POWER 1 and 2 trials for TMC114/r.[2,4]

Design and conduct of RESIST and POWER trials

- The RESIST and POWER trials all recruited treatment-experienced patients with screening HIV RNA >1,000 copies/mL and at least one primary PI mutation based on the IAS-USA list, including D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V and L90M.[1,2,4] In the RESIST trials, patients with two or more mutations at positions 33, 82, 84 and 90 were excluded; patients with these mutations were included in the POWER trials.
- In all trials, an optimised background regimen (OBR) of NRTIs with optional ENF was chosen, based on treatment history and screening resistance analysis (Virco method). In the RESIST trials, NNRTIs could also be included in the OBR.[5]
- For all the trials, the control arm was OBR plus investigator-selected PI treatment (selected using the same Virco resistance methods across the trials). In the RESIST trials, only single-boosted PIs were permitted; patients could use dual-boosted PIs in the POWER trials.
- In the RESIST trials, a standard dose of TPV/r (500/200mg bid) was compared with the CPI arm. In the POWER trials, four different doses of TMC114/r were evaluated. Only the results from the 600/100mg bid dose of TMC114/r (selected for Phase III development in treatment-experienced patients[2,4]) are included in this analysis.
- The primary study endpoint for all trials was the proportion of patients with at least 1 $\log_{10}$ reduction in HIV RNA at Week 24, using the standard ITT FDA algorithm time-to-loss of virological response (TLOVR).

Methods

- Summary baseline and Week 24 efficacy data were extracted from publicly available reports and regulatory summaries for the RESIST and POWER trials.
- The following efficacy parameters were included, using ITT methods
  - ≥1 $\log_{10}$ reduction in HIV RNA (TLOVR)
  - HIV RNA <50 copies/mL at Week 24 (TLOVR)
  - HIV RNA <400 copies/mL at Week 24 (TLOVR)
  - $\log_{10}$ reduction in HIV RNA at Week 24 (NC=F [POWER]; LOCF [RESIST])
  - mean rise in CD4 cell count at Week 24 (LOCF).
- The measures of efficacy were compared across the trials to determine whether the treatment benefit of TMC114/r over CPI in the POWER trials was greater than (outside the 95% CI) the corresponding benefit of TPV/r over CPI in the RESIST trials.
- The justification for this analysis was as follows
  - the combined RESIST and POWER trials include all randomised clinical trial data available for these two PIs
  - the protocol inclusion criteria, design, primary analysis and choice of OBR are very similar across the four trials.
- One subgroup analysis was conducted to control for use of enfuvirtide (ENF) in the trials, analysing patients using ENF for the first time (ENF-naïve) versus those not using ENF.

Results

Comparison of baseline characteristics

- The trials were very similar in terms of mean baseline age, gender and race, baseline CD4 count and HIV RNA (Table 1). The median number of IAS-USA mutations was three in each trial. Prior ARV therapy and baseline genotypic and phenotypic PI resistance was also similar across the trials.
- The main differences between the trials were in the choice of drugs in the OBR. In the POWER trials, 23% of patients used a double-boosted PI (relative to 0% in the RESIST trials). There was a higher percentage of lopinavir/ritonavir (LPV/r) use in the RESIST trials (50%) relative to the POWER trials (38%).
- ENF was used by 45% of patients in the POWER trials, with 32% of patients initiating ENF treatment for the first time at randomisation. In the RESIST trials, 25% of patients used ENF; 15% initiated ENF treatment for the first time at randomisation.
- In the RESIST trials, patients with NNRTI-sensitive virus at screening could use NNRTIs in the OBR, which 17% of patients did. NNRTI use was not allowed in the POWER trials.

Table 1. Summary of baseline characteristics of the POWER and RESIST trials.

Parameter	POWER	RESIST
n	201	1,159
Mean age	44	43
Predominant gender (%)	Male (88)	Male (88)
Predominant race (%)	Caucasian (78)	Caucasian (73)
Mean baseline HIV RNA ($\log_{10}$ copies/mL)	4.6	4.8
Median baseline CD4 count (cells/mm^3)	153	155
CDC Class C (%)	39*	56
Prior ARV therapy		
Median number of NRTIs used	5	6
Median number of NNRTIs used	1	1
Median number of PIs used	4	4
Prior ENF use (%)	17	12
PI use in OBR (%)		
LPV	38	50
APV	33	26
SQV	35	20
IDV	3	4
ATV	16	0
NFV	1	0
Double-boosted PI	23	0
Baseline genotypic PI resistance		
Median number of IAS PI mutations	3	3†
Baseline phenotypic fold resistance		
LPV	≥79	87
APV	19	13
SQV	32	24
TPV	1.8	1.7
ENF use in the OBR (%)		
Total use	45	25
Naïve (first) use	32	15
NNRTI use in the OBR (%)		
Total use	0	17

For POWER trials N = TMC114/r 600/100mg bid dose patients plus CPI patients
*At time of diagnosis
†Those with two or more mutations at positions 33, 82, 84 and 90 were excluded from the RESIST trials
APV = amprenavir; SQV = saquinavir; IDV = indinavir; ATV = atazanavir; NFV = nelfinavir

Comparison of efficacy between TMC114/r and TPV/r trials

- For the POWER and RESIST trials, the 24-week efficacy of the CPI arms was very similar between the two trials when measured as either ≥1 $\log_{10}$ reduction in HIV RNA, HIV RNA suppression to below 400 or 50 copies/mL, continuous $\log_{10}$ reduction, or mean rise in CD4 count.
- When analysed as individual trials, the RESIST studies showed a statistically significant benefit for TPV/r over CPI in terms of all the efficacy parameters; similarly, the TMC114/r 600/100mg bid arm of the POWER trials showed a statistically significant benefit over CPI for the main efficacy parameters (Figure 1).
- The treatment benefit of TMC114/r versus CPI in the POWER trials was larger than the corresponding benefit of TPV/r over CPI in the RESIST trials, for the endpoints of ≥1 $\log_{10}$ reduction in HIV RNA, HIV RNA <400 copies/mL, HIV RNA <50 copies/mL and CD4 count increase. In each case, the estimates of treatment benefit for TMC114/r versus CPI were greater than the 95% CIs of the treatment benefits for TPV/r versus CPI (Table 2).
- For the subgroup of ENF-naïve patients, the treatment benefit of TMC114/r over CPI was again greater than the benefit of TPV/r, for the endpoints of ≥1 $\log_{10}$ reduction in HIV RNA and HIV RNA <50 copies/mL (Table 3). For the subgroup of patients who did not use ENF in their OBR, there was also a greater treatment benefit for TMC114/r with the ≥1 $\log_{10}$ reduction endpoint. Data were not available from the two sets of trials for other endpoints in these subgroups.

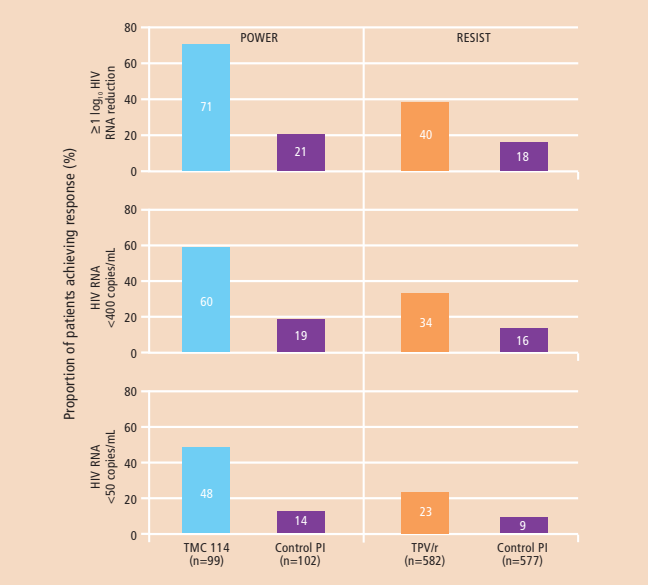

Figure 1. Week 24 virological efficacy in POWER and RESIST trials.

- For ENF-naïve patients in the POWER trials, a ≥1 $\log_{10}$ reduction in HIV RNA was achieved by 57% more [95% CI: 38–77%] patients receiving TMC114/r compared with those receiving CPI. For non-ENF-naïve patients, this figure was 48% [95% CI: 34–62%].
- In the RESIST trials, the proportion of ENF-naïve patients receiving TMC114/r and achieving a ≥1 $\log_{10}$ reduction in HIV RNA was 34% higher [95% CI: 23–46%] than the proportion of ENF-naïve CPI patients. For non-ENF-naïve patients, this figure was 21% [95% CI: 15–28%].

Table 3. Week 24 efficacy according to enfuvirtide (ENF) use and benefit of TMC114/r or TPV/r over CPI in the POWER and RESIST trials.

	POWER		RESIST	
Parameter	TMC114/r	CPI	TPV/r	CPI
ENF-naïve (n)	33	32	145	112
ENF not used (n)	54	60	368	390
≥1 $\log_{10}$ HIV RNA reduction (%)				
ENF-naïve	88	31	64	30
ENF not used	65	17	40	19
HIV RNA <50 copies/mL (%)				
ENF-naïve	64	16	36	14
ENF not used	46	13	data not available	

Conclusions

- The POWER and RESIST trials were very similar in design, inclusion criteria, primary efficacy endpoint and selection of the OBR and CPI treatment. The baseline characteristics showed similar profiles between the trials in terms of age, gender, race, baseline HIV RNA and CD4 count and genotypic PI resistance.
- This meta-analysis of the POWER and RESIST trials suggests that the ARV efficacy of TMC114/r is greater than TPV/r in highly treatment-experienced patients, in terms of HIV RNA suppression and CD4 increases at Week 24.
- The 24-week efficacy results in the CPI arms of the POWER and RESIST trials were also very similar, despite some differences between the trials in the choice of CPIs and in the use of ENF and NNRTIs in the OBR.
- Both TMC114/r and TPV/r showed statistically significant benefits over CPI treatment in the individual studies,[1,2,4] but the meta-analysis showed the size of the treatment benefit of TMC114/r to be greater than for TPV/r.
- The main difference between the trials was in the use of ENF. However, for the subgroups of patients in the POWER and RESIST trials who either used ENF for the first time or did not use ENF at all, there were also greater treatment responses for TMC114/r compared with TPV/r.

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Table 2. Benefit of TMC114/r or TPV/r over CPI in Week 24 efficacy data from the POWER and RESIST trials.

	POWER			RESIST		
Parameter	TMC114/r	CPI	TMC114/r benefit [95%CI]	TPV/r	CPI	TPV/r benefit [95% CI]
n	99	102	-	582	577	-
≥1 $\log_{10}$ HIV RNA reduction (%)	71	21	+50 [39–61]	40	18	+22 [17–27]
HIV RNA <400 copies/mL (%)	60	19	+41 [30–52]	34	16	+18 [13–23]
HIV RNA <50 copies/mL (%)	48	14	+34 [22–44]	23	9	+14 [10–18]
Log_{10} HIV RNA reduction (SD for POWER trials)	–1.90 (1.25)	–0.49 (0.89)	–1.41 [1.14–1.68]	–0.8	–0.25	–0.55 [0.43–0.67]
Mean CD4 count rise (cells/mm^3) (SD for POWER trials)	+98 (120)	+17 (107)	+81 [52–110]	+34	+4	+30 [19–42]

SD = standard deviation

Presented at the 12th Annual Conference of the British HIV Association (BHIVA), 29 March–1 April 2006, Brighton, UK.