MOPEB042

GRACE (Gender, Race And Clinical Experience): 48-Week Results of Darunavir/r-based Therapy in the Largest Trial in North America to Focus on Treatment-experienced Women

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Introduction

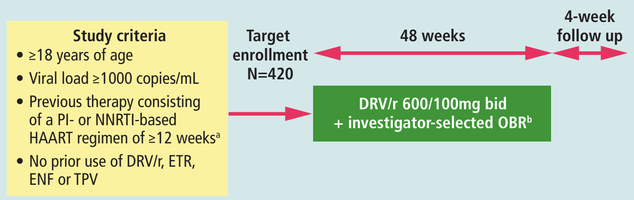
- Women account for an increasing proportion of patients living with HIV/AIDS in the United States (US)[1,2], yet data on the efficacy and safety of antiretrovirals (ARVs) in women are limited
  - Several challenges, including socioeconomic factors, have led to difficulties in recruiting and retaining women in ARV clinical trials
- Darunavir (DRV; PREZISTA®), a protease inhibitor (PI) combined with a low dose of ritonavir (DRV/r), has been approved for use in the US as a therapeutic option for treatment-experienced, treatment-naïve and pediatric (aged 6 to <18 years) HIV-infected patients[3]
- We report 48-week results from the primary analysis of the GRACE (Gender, Race And Clinical Experience) trial, which was designed to enroll a high proportion of treatment-experienced women, in order to assess sex-based differences in the efficacy and safety of DRV/r-based therapy
  - Analyses by race will be presented elsewhere

Methods

Study design and treatment

- Open-label, single-arm, Phase IIIb study conducted at 65 sites across the US, Puerto Rico and Canada for 48 weeks (**Figure 1**)
- Samples taken at screening and at virologic failure (VF) were analyzed for resistance by Virco®TYPE HIV-1 genotype and predicted phenotype analysis (Virco BVBA, Mechelen, Belgium)

Figure 1. Study design



[a]Patients were allowed to enter the study on treatment interruption of ≥4 weeks; [b]Investigator-selected NRTIs and NNRTIs were allowed; ENF, TPV or agents from novel classes were not allowed; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HAART, highly-active antiretroviral therapy; DRV/r, darunavir/ritonavir; ETR, etravirine; ENF, enfuvirtide; TPV, tipranavir; bid, twice daily; OBR, optimized background regimen

Efficacy evaluations

- The primary endpoint was virologic response (HIV-1 RNA <50 copies/mL) at Week 48
  - The primary objective was to compare sex-based differences in response rates
- Secondary endpoints included:
  - CD4+ count change from baseline to Week 48
  - Virologic failure (confirmed viral load [VL] >50 copies/mL) rates and development of new resistance upon failure

Safety evaluations

- Adverse events (AEs), serious AEs and study discontinuations due to AEs were recorded throughout the study
- Clinical laboratory abnormalities were determined according to the sponsor-enhanced Division of AIDS grading severity list
- A *post-hoc* analysis was conducted to determine if reasons for discontinuation differed by sex

Patient population and statistical analysis

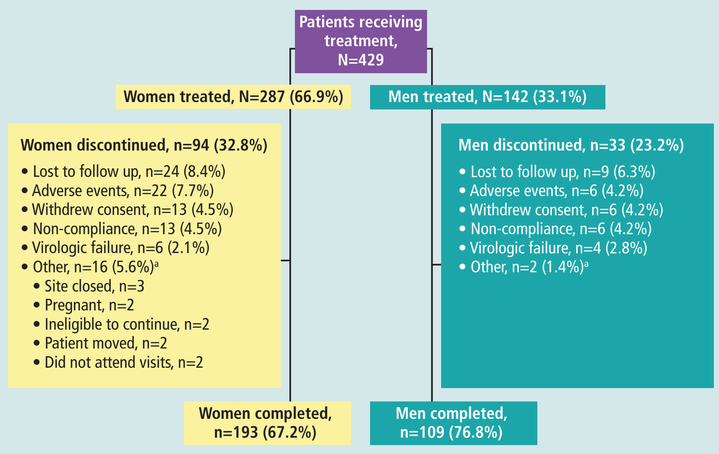
- To meet the recruitment goal of 420 patients (approximately 70% female, 30% male) and ensure approximately equal race distribution between genders, each site was required to enroll three women before enrolling a man, and the number of Caucasian men enrolled was limited
  - Sample size was determined based on a non-inferiority design with a maximum allowable difference for women versus men of ≤15% with a one-sided significance level of α=0.025 and 80% power; 15% was considered *a priori* to be a clinically relevant difference in response
- Efficacy and safety endpoints were analyzed for the intent-to-treat (ITT) population, defined as all enrolled patients who received at least one dose of study medication
  - Virologic response was also calculated for the non-VF censored population, which censors patients who discontinued the study for reasons other than VF
- Virologic response was reported using the time-to-loss of virologic response (TLOVR) algorithm
- Sex-based differences in response rates were derived from logistic regression models that included sex, as well as covariates for baseline VL and CD4+ count
- Changes in CD4+ count from baseline were evaluated by analysis of covariance, including sex, baseline VL and baseline CD4+ count as factors
- Safety endpoints and resistance determinations were analyzed descriptively according to sex

Results

Patient population and baseline characteristics

- A total of 429 patients were enrolled in GRACE and received at least one dose of study drug (287 women; 142 men; **Figure 2**)
- At baseline, women on average were younger and tended to have less advanced disease, less resistance and be less treatment experienced compared with men (**Table 1**)
- The optimized background regimen (OBR) for women and men, respectively, included tenofovir (83.3% and 85.9%), emtricitabine (77.0% and 77.5%), etravirine (40.4% and 61.3%), zidovudine (17.4% and 23.9%) and lamivudine (10.5% and 11.3%)
  - The mean (standard deviation) phenotypic sensitivity score of the OBR was 2.0 (0.65) and 2.0 (0.81) in women and men, respectively
- A total of 193 (67.2%) women and 109 (76.8%) men completed the trial with mean (standard error) treatment durations of 38.5 (0.99) and 41.9 (1.20) weeks, respectively
  - The rate of treatment discontinuation was higher in women (n=94 [32.8%]) compared with men (n=33 [23.2%]; *P*<.05)
  - The primary reasons for study discontinuation were loss to follow up and AEs (**Figure 2**); there were no trends toward a specific type of AE driving discontinuations in either group
  - No individual AE led to discontinuation in more than two patients

Figure 2. Study disposition



[a]'Other' classification was selected by the investigator as reason for discontinuation; 'Other' reasons for discontinuation that each occurred in one woman only were sponsor's decision, safety (older patient taking too many concomitant medications), no decrease in viral load, time restraints on visit attendance and new antiretroviral regimen started in favor of study medication; 'Other' reasons for discontinuation that each occurred in one man only were ineligibility to continue treatment and site closure

Table 1. Baseline characteristics and demographics

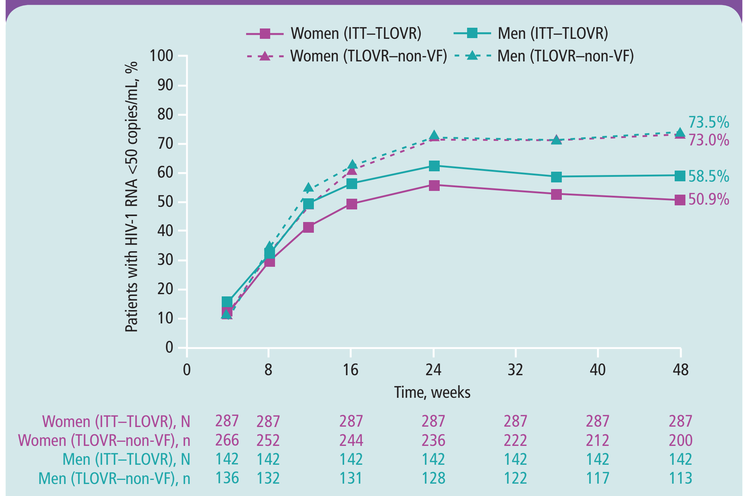
Parameter	Women N=287	Men N=142
Mean (SD) age, years	42 (10.6)	45 (9.0)
Race/ethnicity, n (%)[a]		
Black	191 (66.6)	73 (51.4)
Hispanic/Latino	60 (20.9)	36 (25.4)
Caucasian	34 (11.8)	31 (21.8)
Other	2 (0.7)	2 (1.4)
Mean (SD) BMI, kg/m^2	28.2 (7.41)	25.4 (5.06)
Mean (SD) duration of infection, years	10.9 (5.36)	12.2 (5.84)
Mean (SD) viral load, $\log_{10}$ copies/mL	4.7 (0.88)	4.7 (0.86)
Median (range) CD4+ count, cells/mm^3	210 (1, 868)	175 (2, 1125)
CDC Class C, n (%)[a]	102 (35.5)	67 (47.2)
Entry on treatment interruption, n (%)	100 (34.8)	51 (35.9)
Prior use of ≥2 PIs, n (%)	168 (58.5)	92 (64.8)
>1 IAS-USA major PI mutations, n (%)[b]	77 (27.0)	57 (40.1)
Hepatitis B surface antigen (positive), n (%)	12 (4.2)	7 (4.9)
Hepatitis C antibody (positive), n (%)	39 (13.6)	25 (17.6)

[a]Significantly different for women and men (*P*<.05); [b]By Virco®TYPE; SD, standard deviation; BMI, body mass index; CDC, Centers for Disease Control and Prevention; PI, protease inhibitor; IAS, International AIDS Society

Efficacy

- At Week 48 in the ITT–TLOVR analysis, virologic response rate was higher in men than women; in the non-VF censored population, response rates were similar between men and women (**Figure 3**)
  - When adjusted for baseline VL and CD4+ count, the difference in response rates between women and men was –9.6% (95% confidence interval [CI]: –19.9%, 0.7%) in the ITT–TLOVR analysis and –3.9% (95% CI: –13.9%, 6.0%) in the TLOVR–non-VF analysis
- The rate of VF was 28.6% (n=82) in women and 28.2% (n=40) in men

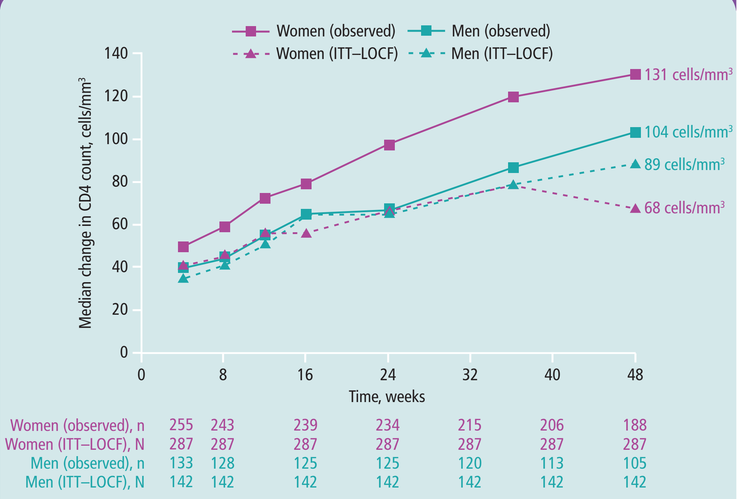
Figure 3. Confirmed virologic response in intent-to-treat and non-virologic failure censored populations[a]



[a]The 95% confidence interval (CI) crossed zero for both ITT and non-VF censored analyses; The 95% CI only included –15% in the ITT–TLOVR analysis; ITT, intent-to-treat; TLOVR, time-to-loss of virologic response; VF, virologic failure

- The median change from baseline in the observed CD4+ count was higher in women than men (**Figure 4**)
- The median change from baseline in CD4+ count for the ITT–last observation carried forward analysis was similar in women and men (**Figure 4**)

Figure 4. Median change from baseline over time in CD4+ cell count in observed case and last observation carried forward analyses[a]



[a]The least-squares mean difference between sexes in the observed and ITT–LOCF analyses, adjusted for baseline viral load and CD4+ count, was 34 cells/mm^3 (95% confidence interval [CI]: 0.4, 68; *P*=.047) and 11 cells/mm^3 (95% CI: –18, 39; *P*=>.05), respectively; ITT, intent-to-treat; LOCF, last observation carried forward

Resistance

- Patients developing new International AIDS Society-USA major PI resistance-associated mutations (RAMs) or new DRV RAMs (**Table 2**) had substantial resistance at baseline, with 1–6 major PI RAMs present[4]

Table 2. Number of patients with new treatment-emergent resistance-associated mutations

Mutations	Women[a,b]	Men[a,b]
IAS-USA major PI RAMs, n (%) (V32I, M46I(2), M46I/L, L33F and I50V(2))	2 (7.4)	2 (11.8)
IAS-USA NRTI RAMs, n (%)	2 (7.4)	2 (11.8)
DRV RAMs, n (%) (V32I, L33F, I50V(2) and L89V)	1 (3.7)	2 (11.8)

[a]Out of 82 women and 40 men with confirmed virologic failure (HIV-1 RNA >50 copies/mL), 27 and 17, respectively, had genotypes available at baseline and virologic failure; [b]Genotype determined only for patients with HIV-1 RNA >1000 copies/mL; IAS, International AIDS Society; PI, protease inhibitor; RAM, resistance-associated mutation; NRTI, nucleoside reverse transcriptase inhibitor; DRV, darunavir

Safety

- Overall, 259 (90.2%) women and 118 (83.1%) men experienced at least one AE (**Table 3**)
  - The majority of AEs were mild-to-moderate in severity
  - In total, 134 (46.7%) women and 61 (43.0%) men experienced at least one AE considered by the investigator to be at least possibly related to DRV/r
- The most common AEs were nausea (women, 24.4%; men, 14.1%), diarrhea (women, 16.4%; men, 22.5%), upper respiratory tract infection (women, 11.1%; men, 7.7%) and vomiting (women, 11.5%; men, 6.3%)
- Serious AEs were reported in 47 (16.4%) women and 33 (23.2%) men; the most commonly reported were pneumonia (2.6% overall) and *Pneumocystis jiroveci* pneumonia (1.2% overall)
  - Four deaths were reported; all were considered unrelated to DRV/r by the investigator

Table 3. Summary of adverse events

Adverse events, n (%)	Women N=287	Men N=142
Patients with ≥1 AE	259 (90.2)	118 (83.1)
Patients with ≥1 SAE	47 (16.4)	33 (23.2)
Patients with ≥1 AE at least possibly related to DRV/r	134 (46.7)	61 (43.0)
Patients with ≥1 grade 2–4 AE at least possibly related to DRV/r[a,b]	80 (27.9)	38 (26.8)
Diarrhea	13 (4.5)	7 (4.9)
Nausea	15 (5.2)	4 (2.8)
Rash	6 (2.1)	4 (2.8)
Weight increase	5 (1.7)	3 (2.1)
Vomiting	4 (1.4)	3 (2.1)
Grade 3–4 laboratory abnormalities		
Total cholesterol (grade 3 only)	10 (4.6)	5 (4.2)
Triglycerides	1 (0.5)	11 (9.2)
Aspartate aminotransferase	8 (3.0)	7 (5.1)
Alanine aminotransferase	6 (2.2)	4 (2.9)
Hyperglycemia	6 (2.2)	4 (2.9)
Lipase	5 (1.9)	5 (3.7)
Pancreatic amylase	4 (1.5)	6 (4.4)
Hyperuricemia	0	4 (2.9)
Plasma prothrombin time	0	4 (4.4)

[a]Occurring in ≥2% of patients in either group; [b]Excluding laboratory abnormalities reported as AEs; No grade 3 or 4 creatinine elevations were reported; AE, adverse event; SAE, serious adverse event; DRV/r, darunavir/ritonavir

Discussion

- In the ITT–TLOVR analysis, which treats all study discontinuations as failures, the difference in virologic response rates between men and women was 9.6% (CI: –19.9%, 0.7%) at Week 48
  - After accounting for differential rates of discontinuation for men and women due to reasons other than VF, the response rates for men and women were similar
- Women had significantly higher increases in CD4+ count compared with men in the observed analyses, as noted in previous ARV trials
- Treatment with DRV/r was similarly tolerated between women and men, with no unexpected AEs, based on results from previous trials[5–8]
  - No specific AE was identified as driving discontinuations in either group
- Discontinuations due to loss to follow up, relocation and withdrawal of consent reflect challenges that may be unique to women with respect to clinical trials

Conclusions

- The GRACE study successfully enrolled a high proportion of women and is, to date, the largest study in North America to assess sex-based differences in the efficacy and safety of an ARV regimen
- Overall, the data from GRACE suggest that DRV/r can be used in women and men with similar safety and efficacy outcomes
- Higher rates of discontinuation among women highlight the need for investigation into the retention of women in clinical trials
  - Addressing the unique needs and challenges of women during the screening process and throughout the study may improve study retention
- GRACE provides insight for the development and design of future clinical trials
  - Setting a requirement of enrolling three women to one man appears to be an effective method of increasing the enrollment of women

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