H-919

GRACE (Gender, Race And Clinical Experience): Etravirine (ETR) Subgroup Analysis at Week 48

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Introduction

- The GRACE study was designed to enroll a high proportion of treatment-experienced women infected with HIV-1, thereby helping to address the paucity of data for antiretroviral (ARV) treatment in women
  - GRACE assessed the efficacy and safety of darunavir/ritonavir (DRV/r) plus an investigator-selected optimized background regimen (OBR), which could include etravirine (ETR), over 48 weeks
- Etravirine (INTELENCE™), a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI) active against NNRTI-resistant HIV-1[1], was approved by the United States (US) Food and Drug Administration in 2008 for use in treatment-experienced patients[2]
- Given precautions related to the use of first generation NNRTIs in women, the limited data on ETR use in women, and the high proportion of women who received ETR as a component of their OBR in GRACE, we assessed efficacy, safety and tolerability in the subgroup of patients in GRACE who received ETR

Methods

Study design and treatment

- GRACE was a multicenter, 48-week, open-label, Phase IIIb study conducted in 65 study sites across the US, Canada and Puerto Rico (**Figure 1**)

Figure 1. Study design

[a]Patients were allowed to enter the study on treatment interruption of ≥4 weeks; [b]Investigator-selected nucleoside reverse transcriptase inhibitor, 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

- ETR (200mg, twice daily) was not commercially available at the start of the study, but was made available for use in the OBR if chosen by the investigator to construct an effective treatment regimen
- Selection of the OBR was based on resistance testing (Virco®TYPE HIV-1), and modifications to the OBR were only allowed in the event of toxicity related to an adverse event (AE) or serious AE (SAE)
- Samples taken at screening and at virologic failure (VF) were analyzed for resistance by Virco®TYPE HIV-1 genotype and virtual phenotype analysis (VircoBVBA, Mechelen, Belgium)

Efficacy evaluations

- The aim of this pre-planned analysis was to evaluate virologic response (HIV-1 RNA <50 copies/mL) and safety in women and men who received ETR in GRACE
- Additional efficacy endpoints included:
  - Change in CD4+ count from baseline to Week 48
  - VF (confirmed HIV-1 RNA >50 copies/mL) rates and development of new resistance upon failure

Safety evaluations

- AEs, SAEs and study discontinuations due to AEs were recorded throughout the study
  - AEs of specific interest to ETR were evaluated, including skin-, cardiac-, neuropsychiatric- and hepatobiliary-associated AEs
- Clinical laboratory abnormalities were determined according to the sponsor-enhanced Division of AIDS grading severity list

Statistical analysis

- Virologic response is reported using a time-to-loss of virologic response (TLOVR) algorithm for the following populations
  - Intent-to-treat (ITT) population (patients who took at least one dose of study medication)
  - Non-VF censored population (censors patients from the ITT population who discontinued for reasons other than VF)
- Changes in CD4+ count were evaluated using observed case and last observation carried forward (LOCF) analyses
- Sub-analysis of patients receiving ETR was not powered for comparisons by sex; descriptive statistics are reported

Multivariate analysis (all 429 patients; ITT–TLOVR)

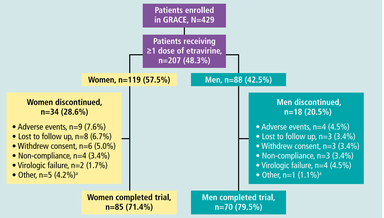
- Factors predictive of virologic response in the total GRACE population were investigated *post hoc*
- Forty-three covariates encompassing patient and disease characteristics, treatment factors, baseline resistance, site characteristics and comorbidities were evaluated in a univariate analysis; covariates significant at the $P<.15$ level in the univariate analyses were considered for the multivariate analysis, with entry and stay criteria of $P<.15$ and $P<.10$, respectively, for inclusion in the final model
- If two or more covariates were highly correlated ($R^2 > .8$), only the most significant in the univariate analyses was included in the multivariate analysis
- Odds ratios were adjusted for other covariates that were included in the final multivariate model

Results

Patient population and baseline characteristics

- Of 429 patients enrolled in GRACE, 207 (119/287 [41.5%] women and 88/142 [62.0%] men) received at least one dose of ETR (**Figure 2**)
  - 203 patients received ETR on study Day 7; two patients each began ETR on Days 8 and 32
- The majority of patients in the ETR subgroup were women of color (**Table 1**)
- Men had more advanced disease than women at baseline (**Table 1**)
- The mean (standard deviation) phenotypic sensitivity score of the OBR, including ETR, was 2.1 (0.81) and 2.0 (0.88) in women and men, respectively
- More women than men discontinued the study (**Figure 2**)
  - The primary reasons for study discontinuation were AEs and lost to follow up
  - No single AE lead to discontinuation in more than 1.5% of patients

Figure 2. Study disposition



[a]'Other' classification was selected by the investigator as a reason for discontinuation

Table 1. Baseline demographics and disease characteristics in the etravirine subgroup

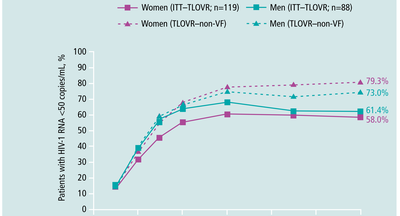
Parameter	Women (n=119)	Men (n=88)	All (n=207)
Mean (SE) age, years	43.9 (1.01)	45.5 (1.02)	44.6 (0.72)
Race/ethnicity, n (%)			
Black	84 (70.6)	49 (55.7)	133 (64.3)
Hispanic	19 (16.0)	17 (19.3)	36 (17.4)
Caucasian	14 (11.8)	20 (22.7)	34 (16.4)
Other	2 (1.7)	2 (2.3)	4 (1.9)
Mean (SE) duration of HIV infection, years	12.9 (0.44)	12.2 (0.59)	12.6 (0.36)
Mean (SE) viral load, $\log_{10}$ copies/mL	4.7 (0.09)	4.6 (0.10)	4.6 (0.06)
Median (range) CD4+ count, cells/mm³	202 (1, 780)	162 (3, 1125)	187 (1, 1125)
CDC Class C, n (%)	50 (42.0)	44 (50.0)	94 (45.4)
Median (range) ETR fold change[a,b]	1.4 (0.4, 93.8)	1.4 (0.3, 64.2)	1.4 (0.3, 93.8)
Median (range) DRV fold change[a]	0.6 (0.3, 128.7)	0.6 (0.4, 148.3)	0.6 (0.3, 148.3)
ETR weighted genotypic score ≤2.0[b], n (%)	91 (76.5)	70 (79.5)	161 (77.8)
Hepatitis B surface antigen (positive), n (%)	3 (2.5)	5 (5.7)	8 (3.9)
Hepatitis C antibody (positive), n (%)	12 (10.1)	17 (19.3)	29 (14.0)

[a]Virco®TYPE HIV-1 resistance analysis; [b]Clinical cut-offs and weighted genotypic score for ETR were not available at time of enrollment and regimen optimization (weighted genotypic scores were determined *post hoc*); SE, standard error; CDC, US Centers for Disease Control and Prevention; ETR, etravirine; DRV, darunavir

Efficacy

- Overall virologic response rates were 59.4% and 76.4% in the ITT and non-VF censored populations, respectively, at Week 48
- Virologic response rates in the ITT and non-VF censored populations were similar for women and men (**Figure 3**)
- The rate of confirmed VF was 21.0% (n=25) in women and 29.5% (n=26) in men
  - Not all patients that experienced VF discontinued the trial; rates of discontinuation due to VF (**Figure 2**) were lower than the overall rates of VF

Figure 3. Virologic response in intent-to-treat and non-virologic failure censored populations

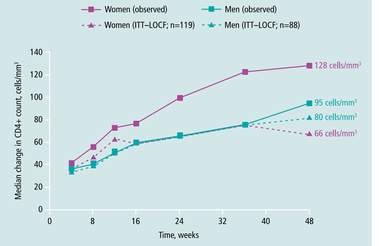


Women (TLOVR–non-VF), n	112	104	101	98	94	91	87
Men (TLOVR–non-VF), n	86	86	86	85	81	77	74

ITT, intent-to-treat; TLOVR, time-to-loss of virologic response; VF, virologic failure

- The median changes in CD4+ count from baseline to Week 48 in the observed and LOCF analyses were +106 and +73 cells/mm³, respectively
- The median change in CD4+ count from baseline was higher in women than men in the observed analysis, but similar in the LOCF analysis (**Figure 4**)

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



Women (observed), n	108	97	101	97	93	89	80
Men (observed), n	85	84	82	83	80	73	67

ITT, intent-to-treat; LOCF, last observation carried forward

Multivariate analysis (all 429 patients; ITT–TLOVR)

- In a *post hoc* multivariate analysis of all patients enrolled in GRACE, inclusion of ETR in the OBR was one of the factors predictive of virologic response (**Table 2**)

Table 2. Factors predictive of virologic response from the multivariate analysis of the total GRACE population (ITT)

Covariate	Adjusted OR	*P* value	95% CI
Improved response			
Adherence ≥95%	2.98	<.0001	1.92, 4.65
Lower baseline viral load[a]	1.81	<.0001	1.39, 2.34
Race/ethnicity other than black	1.79	.0093	1.15, 2.76
Older age[a]	1.03	.0184	1.00, 1.05
No GI medical history	1.65	.0252	1.06, 2.55
Participation at study site with limited clinical trial experience	1.89	.0358	1.04, 3.44
ETR in OBR	1.56	.0424	1.02, 2.38

[a]Continuous; ITT, intent-to-treat; OR, odds ratio; CI, confidence interval; GI, gastrointestinal; ETR, etravirine; OBR, optimized background regimen

Resistance

- Patients with ETR weighted genotypic scores of 0–2 at baseline were more likely to respond than patients with higher scores (**Table 3**)
- Of 51 patients with confirmed VF, 20 had paired genotypes at baseline and VF (patients with HIV-1 RNA >1000 copies/mL at failure)
  - Six patients (30%) developed treatment-emergent ETR resistance-associated mutations: V90I, L100I, K101P, V179F (n=2), Y181C (n=5) and Y181I

Table 3. Influence of etravirine weighted genotypic score on virologic response (ITT–TLOVR)

Baseline ETR weighted genotypic score	Virologic response, n/N (%)
0–2	101/161 (62.7)
2.5–3.5	17/35 (48.6)
≥4	5/11 (45.5)

ITT, intent-to-treat; TLOVR, time-to-loss of virologic response; ETR, etravirine

Safety

- The most commonly reported SAEs were pneumonia (3.4% overall) and *Pneumocystis jiroveci* pneumonia (2.4% overall)
- Two deaths (pneumonia and lactic acidosis) were reported; they were considered not or doubtfully related to ETR by the investigator
- Hypertriglyceridemia was more common in men than women, and nausea was more common in women than men (**Table 4**)
- Among the AEs of interest, skin-related events were the most common (**Table 4**)
  - The majority of rash-related events were grade 1–2 and no pattern was seen with regard to onset or duration of the events; one patient developed grade 3 maculopapular rash and one patient developed grade 4 urticaria
  - Skin-related events leading to permanent discontinuation of ETR were observed in three (2.5%) women and two (2.3%) men

Table 4. Summary of adverse events and grade 3–4 laboratory abnormalities in the etravirine subgroup

Parameter	Women (n=119)	Men (n=88)	All (n=207)
AEs, n (%)			
Patients with ≥1 AE	112 (94.1)	74 (84.1)	186 (89.9)
Patients with ≥1 SAE	25 (21.0)	22 (25.0)	47 (22.7)
Patients with ≥1 AE at least possibly related to ETR (all grades)	65 (54.6)	30 (34.1)	95 (45.9)
Grade 2–4 AEs at least possibly related to ETR[a,b], n (%)			
All	41 (34.5)	20 (22.7)	61 (29.5)
Nausea	12 (10.1)	2 (2.3)	14 (6.8)
Rash (preferred term)	5 (4.2)	3 (3.4)	8 (3.9)
Diarrhea	3 (2.5)	4 (4.5)	7 (3.4)
Rash, maculopapular	2 (1.7)	3 (3.4)	5 (2.4)
Vomiting	3 (2.5)	1 (1.1)	4 (1.9)
Weight gain	3 (2.5)	1 (1.1)	4 (1.9)
Fatigue	3 (2.5)	1 (1.1)	4 (1.9)
Hypertension	3 (2.5)	0	3 (1.4)
Headache	0	2 (2.3)	2 (1.0)
AEs of interest to the ETR subgroup, n (%)			
Skin-associated	32 (26.9)	18 (20.5)	50 (24.2)
Rash-associated	25 (21.0)	14 (15.9)	39 (18.8)
Neuropsychiatric-associated	28 (23.5)	17 (19.3)	45 (21.7)
Cardiac-associated	11 (9.2)	6 (6.8)	17 (8.2)
Hepatobiliary-associated	6 (5.0)	11 (12.5)	17 (8.2)
Grade 3–4 laboratory abnormalities[b], n (%)			
Liver enzymes			
AST	3 (2.7)	5 (6.0)	8 (4.1)
ALT	3 (2.7)	2 (2.4)	5 (2.6)
Hyperglycemia	2 (1.8)	3 (3.6)	5 (2.6)
Lipids			
Total cholesterol	7 (8.0)	5 (6.7)	12 (7.4)
Triglycerides	1 (1.1)	7 (9.3)	8 (4.9)
Hyperuricemia	0	3 (3.6)	3 (1.5)
Lipase	2 (1.8)	3 (3.6)	5 (2.6)
Pancreatic amylase	2 (1.8)	3 (3.6)	5 (2.6)

[a]Excludes lab abnormalities reported as AEs; [b]Occurring in ≥2% of patients in either group; AE, adverse event; SAE, serious adverse event; ETR, etravirine; AST, aspartate aminotransferase; ALT, alanine transaminase

Discussion

- More than 200 patients, including 119 women, enrolled in the GRACE study received ETR as part of the investigator-selected OBR
- At Week 48 in this subgroup:
  - The virologic response rates (59.4% in ITT–TLOVR and 76.4% in TLOVR–non-VF censored) were slightly higher than the response rates for the overall GRACE population (53.4% and 73.2%, respectively)[5]
  - Similar virologic response rates were observed for women and men in the ETR subgroup
- A multivariate analysis performed on the overall GRACE population, which accounts for differences in baseline characteristics, confirmed that the inclusion of ETR in the OBR was significantly associated with improved response in GRACE
- Both women and men in the ETR subgroup demonstrated an increase in CD4+ count over the course of the study
  - In the observed analysis, women had higher median increases in CD4+ count than men
- Overall, a favorable safety and tolerability profile was observed in the ETR subgroup, with little difference observed between sexes with regards to the majority of AEs
  - Nausea was more common in women and hypertriglyceridemia was more common in men
- The incidence of AEs in the ETR subgroup was similar to the overall GRACE population, with the exception of rash (all grades/types; regardless of causality), which was seen in more women in the ETR subgroup (21.0%) than women in the overall GRACE population (15.3%)[6]
- The incidence of rash in women in the ETR subgroup (all grades/types) regardless of causality was lower than the incidence seen in the DUET studies at Week 48 (30.0%)[7]
  - Sex-based differences in rash incidence were not as notable in GRACE (21.0% in women and 15.9% in men) as they were in DUET (30.0% [n=60] and 18.0% [n=539], respectively)[7]

Conclusions

- ETR, as part of an ARV regimen in the GRACE study, was efficacious and associated with improved virologic outcomes
- Similar virologic outcomes were observed among men and women receiving ETR; women who stayed in the study had a better immune response than men
- Although the incidence of AEs was generally similar among men and women, these data suggest that nausea is more common in women than men, while triglyceride elevations are more common in men than women; the incidence of rash in women may be lower than that suggested in earlier studies

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