WEPE011

METABOLIK (Metabolic Evaluation in Treatment-naïves Assessing the impact of two BOosted protease inhibitors on LIpids and other marKers): Comparison of the Metabolic Effects of Darunavir/ritonavir versus Atazanavir/ritonavir over 12 Weeks

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Introduction

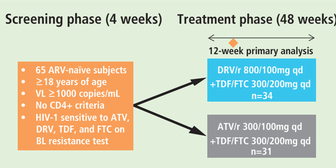
- There is growing evidence that the risk of serious conditions, including cardiovascular, kidney and liver disease and non–AIDS-defining malignancies, is higher in individuals with HIV infection compared with uninfected individuals[1]
  - HIV-induced activation of inflammatory and coagulation pathways has been proposed as a partial explanation[2]
- Antiretroviral (ARV) agents, including protease inhibitors (PIs), may additionally contribute to metabolic complications and increased cardiovascular risk associated with HIV infection[1]
  - Some boosted PIs have been associated with worsening of lipid parameters, increased inflammation and insulin resistance[3-8]
- Previous studies have suggested that darunavir has a favorable lipid profile in treatment-naïve subjects[9]
- In the TMC114-C159 trial, the metabolic effects of darunavir boosted with low-dose ritonavir (DRV/r) have been shown to be comparable with those of atazanavir boosted with low-dose ritonavir (ATV/r) in HIV-negative volunteers[10]
- Additionally, DRV/r and ATV/r are listed as components of the preferred PI-containing regimens in the 2009 U.S. Department of Health and Human Services HIV Treatment Guidelines[11]
- We present the Week 12 primary analysis of METABOLIK, a study evaluating metabolic outcomes of DRV/r-based therapy compared with those of ATV/r-based therapy in treatment-naïve, HIV-1–infected adults

Methods

Study design and treatment

- METABOLIK is a 48-week, Phase IV, multicenter, open-label, randomized study **(Figure 1)**
- Subjects were randomized 1:1, stratified by sex, to receive DRV/r or ATV/r
- Use of lipid-lowering agents was prohibited from 28 days prior to baseline through Week 12
  - Use of atorvastatin, rosuvastatin and other lipid-lowering agents was allowed after Week 12

Figure 1. Study design



ARV, antiretroviral; VL, viral load; ATV, atazanavir; DRV, darunavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; BL, baseline; r, low-dose ritonavir; qd, once daily

Study evaluations

- The primary endpoint was the change in triglyceride levels from baseline to Week 12
- Secondary endpoints included changes in:
  - Total cholesterol (TC), high-density lipoprotein (HDL), measured low-density lipoprotein (LDL) and apolipoproteins (apo) A1 and B
  - Glucose levels, insulin levels, and insulin sensitivity, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) method
  - Inflammatory biomarkers: interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α), and high sensitivity C-reactive protein (hs-CRP)
  - Coagulation biomarkers: fibrinogen and d-dimer
  - Bacterial translocation marker: lipopolysaccharide (LPS)
  - Viral load and CD4+ cell count
- Creatinine clearance was investigated throughout the study
- Fasting (8-hr) blood samples for laboratory assessments, including lipids, were conducted at Weeks 4, 8, 12, 24, 36 and 48, as were efficacy evaluations
- Biomarker tests were obtained at Weeks 4, 12, 24 and 48

Statistical analysis

- Subjects who completed Week 12, and who had baseline and at least one post-dose fasting lipid value and no relevant protocol deviations, were evaluated for lipid endpoints (observed values)
- All other endpoints are reported using observed values for the intent-to-treat (ITT) population
- Descriptive statistics are reported for the primary and secondary endpoints

Results

Subject population and baseline characteristics

- 32 of 34 subjects that received DRV/r, and 30 of 31 subjects that received ATV/r, completed Week 12
  - Of these, 28 and 27 subjects in the DRV/r and ATV/r arms, respectively, were evaluable for lipid parameters
    - 4 subjects in the DRV/r arm and 3 subjects in the ATV/r arm were excluded from lipid evaluation due to major protocol deviations that had the potential to affect lipid parameters
- At baseline, DRV/r subjects had higher viral loads, lower median CD4+ counts **(Table 1)** and lower TC levels **(Figure 2)** than ATV/r subjects

Table 1. Baseline demographics and disease characteristics

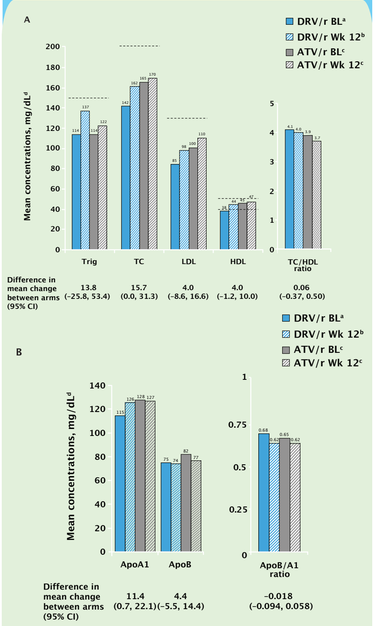
Parameter	DRV/r (n=34)	ATV/r (n=31)
Male, n (%)	29 (85.3)	27 (87.1)
Age, median (range)	36.5 (19.0–58.0)	35.0 (20.0–65.0)
Race, n (%)		
White	21 (61.8)	12 (38.7)
Black	13 (38.2)	17 (54.8)
Asian	0	2 (6.5)
Ethnicity, n (%)		
Hispanic	7 (20.6)	7 (22.6)
Non-Hispanic	27 (79.4)	24 (77.4)
Worst clinical stage of HIV infection, n (%)		
A	30 (88.2)	26 (83.9)
B	4 (11.8)	4 (12.9)
C	0	1 (3.2)
BMI, mean (SD)	23.8 (3.10)	24.5 (3.62)
CD4+ count, median (range) cells/mm^3	267 (10–532)	316 (39–813)
Viral load, mean (SD) $\log_{10}$ copies/mL	5.0 (0.8)	4.6 (0.7)
Viral load, median (range) copies/mL	137,000 (642–2,450,000)	46,100 (397–637,000)

DRV/r, darunavir/low-dose ritonavir; ATV, atazanavir; BMI, body mass index; SD, standard deviation

Lipid evaluations

- Small changes in lipid parameters were noted with DRV/r therapy from baseline to Week 12 **(Figure 2)**
  - Triglycerides increased by a mean of 22mg/dL
  - Total cholesterol increased by a mean of 20mg/dL, while the TC/HDL ratio did not change
- Differences in mean changes were noted between the DRV/r and ATV/r arms in TC and apoA1 **(Figure 2)**
- No differences between arms were noted for changes in the other fasting lipid parameters **(Figure 2)**

Figure 2. Lipid parameters at baseline and Week 12



In Figure 2A, dashed lines represent the National Cholesterol Education Program criteria[12]: Trig ≥150mg/dL, TC ≥200mg/dL, LDL ≥130mg/dL, HDL ≤40mg/dL for men and ≤50mg/dL for women; [a]n=28; [b]n=27; [c]To convert from mg/dL to mmol/L, divide mg/dL value by the following conversion factors: Trig=88.6; TC, LDL or HDL=38.7. To convert apoA1 and apoB from mg/dL to g/L, divide by 100; DRV/r, darunavir/low-dose ritonavir; BL, baseline; Wk, week; ATV/r, atazanavir/low-dose ritonavir; Trig, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CI, confidence interval; Apo, apolipoprotein

Other laboratory, inflammatory and efficacy evaluations

- No clinically relevant changes in fasting glucose, fasting insulin, insulin sensitivity or creatinine clearance were seen with DRV/r therapy or ATV/r therapy from baseline to Week 12 **(Table 2)**

Table 2. Change in glucose, insulin, insulin sensitivity, creatinine clearance, biomarkers and efficacy parameters from baseline to Week 12

	DRV/r[a] BL	DRV/r[a] Change from BL to Wk 12	ATV/r[a] BL	ATV/r[a] Change from BL to Wk 12	Difference in mean change between arms, (95% CI)
Glucose, insulin, and HOMA-IR, mean (SD)					
Glucose, mg/dL	89 (12)	2 (13)	90 (11)	6 (15)	–4.3 (–11.3, 2.8)
Insulin, μIU/mL	6.0 (5.6)	–1.1 (5.0)	8.6 (14.3)	0.7 (18.8)	–1.78 (–8.9, 5.3)
HOMA-IR	1.6 (1.7)	–0.5 (2.0)	2.9 (6.0)	0.1 (7.5)	–0.6 (–4.1, 2.9)
Creatinine clearance, mean (SD)					
Creatinine clearance, mL/min	107.6 (28.7)	–4.6 (15.6)	110.9 (27.9)	–5.3 (16.5)	–0.7 (–7.5, 8.9)
Biomarkers, mean (SD)					
IL-1 beta, pg/mL	0.2 (0.3)	0.01 (0.2)	0.3 (0.3)	–0.01 (0.3)	0.013 (–0.118, 0.143)
IL-6, pg/mL	1.9 (1.9)	–0.6 (2.9)	1.0 (1.3)	1.5 (6.3)	–2.041 (–4.534, 0.451)
hs-CRP, mg/L	3.1 (5.2)	–0.6 (6.0)	2.2 (2.5)	0.7 (4.2)	–1.342 (–4.041, 1.357)
Fibrinogen, g/L	3.3 (1.1)	–0.5 (1.1)	3.2 (0.7)	–0.1 (0.9)	–0.417 (–0.944, 0.110)
TNF-α, pg/mL	4207 (1702)	–1456 (1519)	2957 (727)	–562 (530)	–893.8 (–1499.6, –288.0)
LPS, pg/mL	85 (29)	–3 (38)	87 (31)	–7 (25)	4.656 (–12.727, 22.038)
Efficacy parameters, mean (SD)					
Viral load, $\log_{10}$ copies/mL	5.0 (0.8)	–3.0 (0.8)	4.6 (0.7)	–2.6 (0.7)	–0.35 (–0.74, 0.04)
CD4+ cell count, cells/mm^3	268.3 (144.2)	111.1 (97.3)	326.7 (174.1)	68.3 (134.6)	42.8 (–16.9, 102.6)

[a]ITT-observed (sample size varies by time point and parameter); ITT, intent-to-treat; DRV/r, darunavir/low-dose ritonavir; ATV/r, atazanavir/low-dose ritonavir; BL, baseline; Wk, week; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation; IL, interleukin; hs-CRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor-alpha; LPS, lipopolysaccharide

- Biomarkers generally decreased from baseline to Week 12 in both treatment arms **(Table 2)**
  - The largest decreases were seen in TNF-α and LPS; TNF-α decreased to a greater extent in the DRV/r arm than in the ATV/r arm
- The mean viral load decreased and CD4+ count increased from baseline to Week 12 in both arms **(Table 2)**

Discussion

- Changes in lipids generally occur early in ARV treatment, and this trial of DRV/r in ARV-naïve, HIV-infected subjects demonstrates small changes in lipids over 12 weeks of treatment
  - These results are consistent with results from the ARTEMIS trial, which indicated that DRV/r had a favorable metabolic profile[13]
  - ApoA1 is the primary component of HDL and, therefore, the increase in apoA1 seen in this trial indicates favorable lipid changes in subjects receiving DRV/r-based therapy
- These results support those from the TMC114-C159 trial, in which mean changes in lipid and glucose parameters were also generally small and similar between DRV/r and ATV/r treatment groups[10]
- Activation of inflammatory and coagulation pathways (TNF-α, IL-6, d-dimer and other biomarkers) in HIV-1–infected subjects may contribute to an increased risk of serious non-AIDS conditions relative to HIV-negative subjects[1,2,14-16]
  - Changes in metabolic parameters and inflammatory markers over 12 weeks with DRV/r were comparable with changes observed with ATV/r
  - Decreases in TNF-α and LPS through Week 12 suggest favorable decreases in inflammatory and translocation markers for DRV/r
- Differences in changes in certain parameters between the DRV/r and ATV/r arms may be due to differences in the baseline values of these parameters
  - Larger changes in TC and apoA1 with DRV/r versus ATV/r may be due to lower baseline values of these parameters in the DRV/r arm
  - Similarly, the larger change in TNF-α may be due to the higher baseline value in the DRV/r arm
- Unlike some other PIs, including indinavir and lopinavir/r,[6-8] which have been shown to negatively affect insulin sensitivity, no clinically significant changes were seen in insulin sensitivity in either arm of this study
- No changes in creatinine clearance were seen from baseline to Week 12 in either treatment arm

Conclusions

- Given its favorable metabolic profile and efficacy in HIV-1–infected subjects, DRV/r is a valuable therapeutic option for treatment-naïve subjects and may minimize the risk of metabolic complications
- Changes in metabolic parameters and biomarkers from baseline to Week 12 were comparable for DRV/r- and ATV/r-based therapy; longer-term follow-up of these parameters is planned
- Favorable lipid changes in subjects on highly active ARV therapy support the return-to-health phenomenon observed in subjects undergoing ARV therapy[17]

References

1. Phillips AN, et al. *AIDS*. 2008;22:2409-2418.
2. Neuhaus J, et al. *J Infect Dis*. 2010;201:1788-1795.
3. Friis-Møller N, et al. *New Engl J Med*. 2007;356:1723-1735.
4. Flint OP, et al. *Toxicol Pathol*. 2009;37:65-77.
5. Zhou H, et al. *Atherosclerosis*. 2007;195:e134-143.
6. Noor MA, et al. *AIDS*. 2001;15:F11-18.
7. Noor MA, et al. *AIDS*. 2004;18:2137-2144.
8. Noor MA, et al. *AIDS*. 2002;16:F1-8.
9. Baraldi E, et al. Presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009. Poster MOPEB034.
10. Tomaka F, et al. *HIV Med*. 2009;10:318-327.
11. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 10, 2010.
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. NIH Publication No. 02-5215. September 2002.
13. Mills AM, et al. *AIDS*. 2009;23:1679-1688.
14. Baker J, et al. *J Infect Dis*. 2010;201:285-292.
15. Norris PJ, et al. *AIDS Res Hum Retroviruses*. 2006;22:757-762.
16. Stacey AR, et al. *J Virol*. 2009;83:3719-3733.
17. Riddler SA, et al. *JAMA*. 2003;289:2978-2982.

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