697

Changes In Liver Steatosis After Switching Efavirenz To Raltegravir: The STERAL Study

Juan Macías (1), Dolores Merino (2), Francisco Téllez (3), Federico Pulido (4), Juan González (5), Manuel Márquez (6), Antonio Rivero (7), María Mancebo (1), Juan A. Pineda (1). RIS-HEP09

(1)Hospital Universitario de Valme, (2)Complejo Hospitalario de Huelva, (3)Hospital Universitario Puerto Real, (4)Hospital Universitario Doce de Octubre, (5)Hospital Universitario La Paz, (6)Hospital Universitario Virgen de la Victoria, (7)Hospital Universitario Reina Sofía

Correspondence to:
Dr. Juan Macías
U. Enfermedades Infecciosas y Microbiología.
Hospital Univ. de Valme
Avda. Bellavista s/n
41014 Seville
SPAIN
E-mail: juan.macias.sanchez@gmail.com

ABSTRACT

BACKGROUND: Hepatic steatosis (HS) is a cause of liver disease. In addition, steatohepatitis can induce liver fibrosis and accelerate fibrosis progression associated with HCV. As a consequence, the effects of antiretroviral drugs less likely to induce increases in HS in HIV/HCV coinfection need to be investigated. Because of this, we aimed at comparing the impact of switching from efavirenz (EFV) plus two nucleoside analogs (nucs) to rategravir (RAL) plus two nucs versus continuing with EFV plus two nucs on HS among HIV/HCV-coinfected patients.

METHODS: This was a phase 4, open-label, randomized clinical trial (ClinicalTrials.gov: NCT01900015). HIV-infected patients, with or without detectable plasma HCV RNA, on current EFV plus two nucs were randomized 1:1 to switch EFV to RAL (400 mg BID), maintaining nucs unchanged, or to continue with EFV plus two nucs. At baseline (BL), eligible patients should show controlled attenuation parameter (CAP) values ≥238 dB/m, i.e. significant HS. Changes in HS were measured using CAP at BL, 24 and 48 weeks of follow-up.

RESULTS: Overall, 39 patients were included and 19 of them were randomized to switch to RAL. BL CAP values were not significantly different. However, at week 48, median (Q1-Q3) CAP for the RAL group was 250 (221-277) dB/m and 286 (269-314) dB/m for the EFV group (p=0.035). The median (Q1-Q3) of the difference in CAP measurements between BL and week 48 was -20 (-67; 15) dB/m for the RAL arm and 30 (-17; 49) dB/m for the EFV group (p=0.011). CAP values <238 dB/m at week 48 were observed in 9 (47%) patients on RAL and 3 (15%) individuals on EFV (p=0.029).

CONCLUSIONS: After 48 weeks, HIV-infected individuals switching from EFV to RAL showed decreases in the degree of HS, as measured by CAP, compared with those continuing with EFV. In addition, the proportion of patients without significant HS, i.e. with CAP <238 dB/m, after 48 weeks was greater for those who switched from EFV to RAL.

(Updated abstract)

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is frequently observed in HIV-infected patients. NAFLD itself can promote fibrosis progression, evolving to steatohepatitis, on which cirrhosis may develop and hepatocellular carcinoma emerge. HS is linked with metabolic disorders and exposure to certain antiretroviral drugs. The main potential mechanism involved in antiretroviral drug-related HS seems to be mitochondrial toxicity. Thus, the use of nucleoside analogs associated with more severe mitochondrial toxicity, as dideoxynucleoside analogs, has been linked with HS. Efavirenz (EFV) has been related with clinical manifestations of mitochondrial toxicity, such as lipoatrophy. Likewise, EFV enhances fatty accumulation in hepatocyte cell lines in vitro. Moreover, the cumulative use of EFV seemed to be associated with an increased risk of HS progression in HIV/HCV-coinfected patients.

Given the potential of NAFLD for causing advanced liver disease, the effects of antiretroviral drug regimens less likely to induce increases in HS need to be investigated. Drug combinations based on raltegravir (RAL) may fulfill that requirement. In addition, use of RAL was associated with a trend to lower frequency of HS and lesser likelihood of progression of HS, but these associations did not stand up after controlling for metabolic factors. Therefore, the role of RAL preventing the progression of HS, which could be driven by its metabolic safety profile, needs to be clarified in controlled, prospective studies.

OBJECTIVE

To compare the impact of switching from EFV to RAL in patients receiving EFV plus two nucleoside analogs versus continuing with the same therapy on HS as measured by CAP among HIV-infected patients with NAFLD.

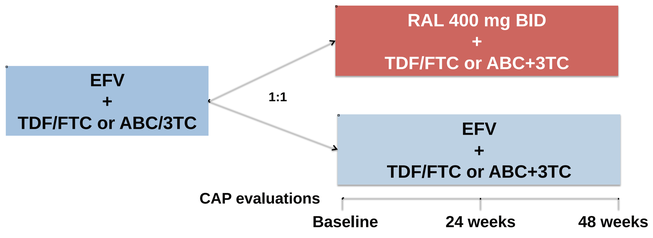
ACKNOWLEDGEMENTS

Unión Europea
Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"

This study has been partially funded by the Merck Sharp & Dome Investigator Studies Program with code MISP#50410", and by the RD12/0017/0012 project as part of the Plan Nacional R+D+I and cofinanced by ISCIII-Subdirección General de Evaluación, the Fondo Europeo de Desarrollo Regional (FEDER). J.M. is the recipient of a grant from the Servicio Andaluz de Salud de la Junta de Andalucía (grant number B-0037). J.A.P. is recipient of an intensification grant from the Instituto de Salud Carlos III (grant number Programa-I3SNS). Raltegravir was provided by Merck Sharp & Dohme de España (Madrid, Spain).

PATIENTS AND METHODS

Trial design: Phase 4, multicenter, open-label, randomized trial.



- Inclusion criteria:
  - To be 18 years of age or older.
  - EFV + TDF/FTC or ABC/3TC for the last ≥6 months.
  - Plasma HIV RNA <50 copies/ml for ≥24 weeks in ≥2 visits.
  - CAP ≥238 dB/m, indicative of the presence of HS involving more than 10% of hepatocytes.
  - Daily alcohol intake <50 g for men and <40 g for women.
- Steatosis evaluation:
  - CAP and liver stiffness were measured using a device with the standard M probe (FibroScan® 502, Echosens, Paris, France).
  - An experienced operator who was blinded for the therapy regimen performed the elastographic measurements.
  - Determinations were considered as valid if at least 10 successful measurements could be achieved, with an interquartile range (IQR) <30% of the median liver stiffness value and a success rate >60%.
- Statistical analysis:
  - Primary variable: The median value of CAP after 48 weeks of follow-up. The median value of CAP at 48 weeks was compared between arms. The median decline in this parameter observed during follow-up was also compared between groups.
  - Chi-square test or Fisher's exact test were used to compare proportions between treatment groups. Mann-Whitney U-test was applied for comparisons of continuous variables between groups.

RESULTS

Characteristics of the patients

Characteristic	Raltegravir group (n=19)	Efavirenz group (n=20)	P-value
Age[1], years	52 (45-55)	48 (47-52)	0.158
Male gender, n (%)	17 (90)	15 (80)	0.939
CD4 cell counts[1], cel/μL	556 (342-856)	582 (371-774)	0.954
CD8 cell counts[1], cel/μL	728 (531-916)	651 (463-952)	0.909
Plasma HIV RNA <50 copies/ml, n (%)	19 (100)	18 (95)	0.515
Detectable HCV RNA, n (%)	14 (74)	12 (68)	0.874
Body mass index[1], Kg/m²	27 (23.9-29.5)	25 (23.7-26.6)	0.503
Fasting plasma glucose[1], mg/dL	96 (88-105)	94 (83-110)	0.603
HOMA[1]	2.4 (1.8-4)	2.2 (1.8-5.4)	0.759
Triglycerides[1], mg/dL	102 (80-136)	117 (88-166)	0.977
Total cholesterol[1], mg/dL	173 (133-185)	174 (159-202)	0.258
LDL-cholesterol[1], mg/dL	83 (63-110)	117 (86-131)	0.081
HDL-cholesterol[1], mg/dL	50 (42-64)	50 (40-62)	0.964
Total cholesterol/HDL ratio[1]	3.2 (2.2-4.5)	3.5 (3.2-4.6)	0.380
ALT[1], IU/mL	32 (24-70)	44 (27-77)	0.283
AST[1], IU/mL	32 (25-53)	37 (25-65)	0.687
GGT[1], IU/mL	73 (57-112)	79 (41-203)	0.813
Total bilirubin[1], mg/dL	0.4 (0.3-0.5)	0.41 (0.31.0.6)	0.194
Waist circumference[1], cm	89 (84-98)	93 (89-97)	0.838
Hip circumference[1], cm	98 (92-103)	95 (93-101)	0.708
Waist/hip ratio[1]	0.95 (0.90-1.0)	0.95 (0.91-1.0)	0.683
Systolic blood pressure[1], mmHg	126 (115-134)	119 (110-130)	0.633

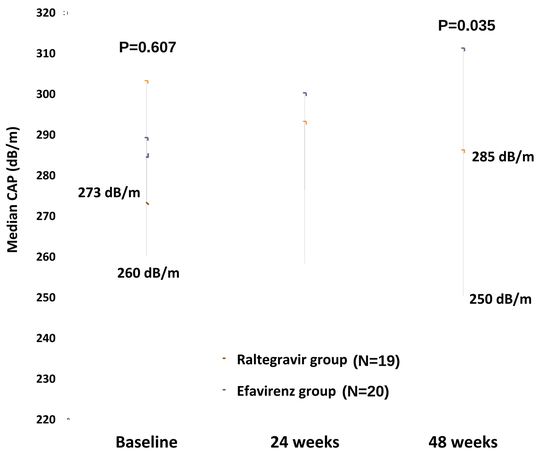
1: Median (IQR)

Changes in lipids among patients without lipid lowering drugs (n=33)

	Median (Q1-Q3) concentration at week 48		Median (Q1-Q3) change in concentration between baseline and week 48		p[1]
	Raltegravir group	Efavirenz group	Raltegravir group	Efavirenz group	
Triglycerides, mg/dL	107 (79-159)	125 (97-238)	-9 (-33; 19)	24 (-4.3; 74)	0.010
Total chol, mg/dL	162 (115-182)	172 (162-192)	-18 (-25; 6.5)	0.5 (-17; 10)	0.094
LDL-chol, mg/dL	88 (61-110)	102 (82-127)	-4 (-12; 4.5)	-1.0 (-8.8; 13)	0.488
HDL-chol, mg/dL	42 (33-54)	50 (43-55)	-8 (-13; -3)	-4.5 (-9; -1.3)	0.191
Total chol/HDL ratio	3.2 (2.6-4.9)	3.8 (3.2-4.5)	0.3 (-0.04; 0.7)	0.2 (-0.1; 0.6)	0.958

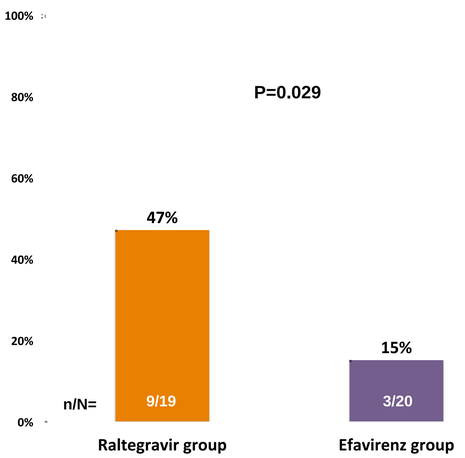
1. P-values for the difference in change from baseline to week 48 between treatment groups.

Median (Q1-Q3) CAP value by treatment group during the follow-up

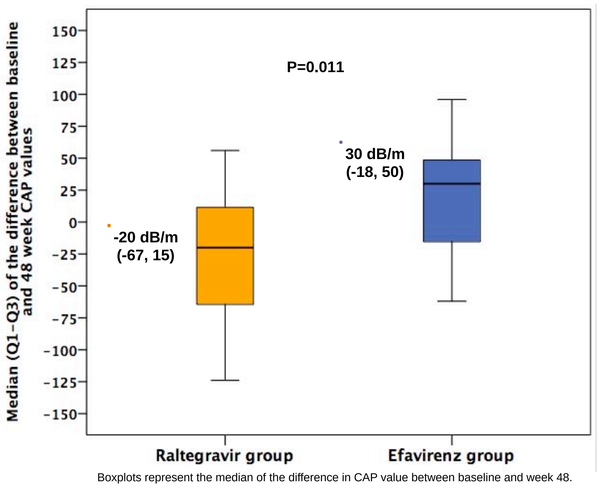


P-values show comparisons between groups of treatment at baseline and at 48 weeks.

Proportion of patients without significant steatosis (CAP <238 dB/m) at week 48

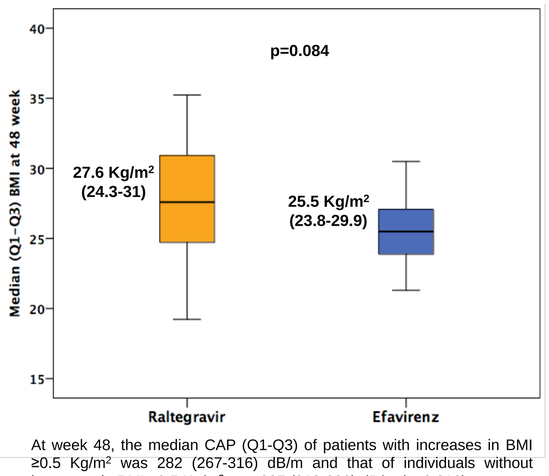


Comparison of median changes in CAP values between baseline and week 48



Boxplots represent the median of the difference in CAP value between baseline and week 48.

Median body mass index (Q1-Q3) by treatment group at 48 weeks



At week 48, the median CAP (Q1-Q3) of patients with increases in BMI ≥0.5 Kg/m² was 282 (267-316) dB/m and that of individuals without increases in BMI ≥0.5 Kg/m² was 237 (213-292) dB/m (p=0.013).

CONCLUSIONS

- **After 48 weeks, HIV-infected individuals switching from EFV to RAL showed decreases in the degree of hepatic steatosis, as measured by CAP, compared with those continuing with EFV.**
- **The proportion of patients without significant of hepatic steatosis, i.e. with CAP <238 dB/m, after 48 weeks was greater for those who switched from EFV to RAL.**