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RAL & DRV PK in Liver Disease (Abstract 10)

Raltegravir and darunavir plasma pharmacokinetic in HIV-1 infected patients with advanced liver disease.

Tommasi C, Nicastri E, Gallo AL, et al.

The pharmacokinetic profiles of darunavir and raltegravir were analysed in 5 HIV/HCV-infected patients with moderate to severe liver disease. Based on the ultrasonographic and histological evaluation, 2 patients had HCV-related chronic active hepatitis, and 3 patients had a diagnosis of cirrhosis (Child Pugh stage B). Trough concentrations were determined 14 and 30 days after starting a raltegravir/darunavir containing regimen. Mean raltegravir and darunavir trough concentrations in the hepatic impairment group was 637 (mean Ctrough in control group: 221±217 ng/ml) and 8519 ng/mL (mean Ctrough in control group: 3236±2183 ng/ml), respectively. In a sub-group analysis, patients with cirrhosis had higher mean raltegravir Ctrough than patients with active non cirrhotic hepatitis (665 vs 581 ng/mL). The mean darunavir Ctrough was consistently higher in cirrhotic than non cirrhotic patients (9820 vs 2016 ng/mL). The data suggest special caution in the use of raltegravir, and especially of darunavir, in patients with moderate to severe liver impairment because of the risk of additive toxicity.

Editorial Comment: This is a small study and additional data will clearly be important to define the impact of liver disease on these drugs.

Sur 43 patients coinfectés /241 non-coinfectés : pas de différence aire sous la courbe, résiduelle

Incidence supérieure d'AES hépatique chez coinfectés

5-6% augmentation ASAT, ALAT, GGT avec 3 grade trois // 2-3% non coinfectés

Conclusion

Effet mineur

Suivi standard des patients coinfectés !!!!!!!!

Hepatic safety and efficacy of raltegravir in patients Co-infected with HIV and HBV or HCV
Poster 662 CROI 2010
Rockstroh

	BENCHMRK (treatment-experienced)				STARTMRK (treatment-naïve)			
	RAL + OBT		Placebo + OBT		RAL + TDF/FTC		EFV + TDF/FTC	
	HBV/ HCV$^+$	HBV/ HCV$^-$	HBV/ HCV$^+$	HBV/ HCV$^-$	HBV/ HCV$^+$	HBV/ HCV$^-$	HBV/ HCV$^+$	HBV/ \HCV$^-$
	n = 77 (PYR=125)	n = 385 (PYR=584)	n = 37 (PYR=33)	n = 200 (PYR=210)	n = 18	n = 263	n = 16	n=266
Percentage (rate/100 PYR)* with lab abnormalities of grade 3 or 4 and increased grade from baseline								
AST increase	10.4 (6.4)	3.6 (2.4)	2.8 (3.0)	4.5 (4.3)	11.1	2.3	6.3	2.3
ALT increase	13.0 (8.0)	3.6 (2.4)	8.3 (9.1)	3.0 (2.9)	5.6	1.5	12.5	1.9

Table 6. Liver Function Tests and Hepatobiliary Clinical Events, Phase III Studies

Adverse Experience (AE)	STARTMRK		BENCHMRK			
	Raltegravir N=281	Efavirenz N=282	Raltegravir N=462 PYR=708		Placebo N=237 PYR=244	
	%	%	%	Rate†	%	Rate†
Overall Population: Liver Function Tests						
Grade 3 or 4 ALT	1.8	2.5	5.2	3.4	3.8	3.7
Grade 3 or 4 AST	2.8	2.5	4.8	3.1	4.2	4.1
Grade 3 or 4 Total Bilirubin	0.7	0.0	3.7	2.4	2.5	2.5
Discontinued Due to Laboratory AE of ALT/AST/Bilirubin	0.0	0.7	0.2	0.1	0.0	0.0
Overall Population: Hepatobiliary Clinical Events‡						
All AEs	0.7	0.4	1.1	N/D	1.3	N/D
Drug-related§ AEs	0.4	0.4	0.9	N/D	1.3	N/D
Serious AEs	0.0	0.0	0.2	N/D	0.4	N/D
Discontinued Due to Clinical AEs	0.0	0.0	0.2	N/D	0.0	N/D
Patients With Hepatitis B and/or C Co-Infection¶: Liver Function Tests						
Grade 3 or 4 ALT	5.6	12.5	13.0	8.0	8.1	9.1
Grade 3 or 4 AST	11.1	6.3	10.4	6.4	2.7	3.0
Grade 3 or 4 Total Bilirubin	0.0	0.0	3.9	2.4	5.4	6.0
Patients With Hepatitis B and/or C Co-Infection¶: Hepatobiliary Clinical Events						
All AEs	0.0	0.0	1.3	N/D	0.0	N/D
Drug-related§ AEs	0.0	0.0	1.3	N/D	0.0	N/D
Serious AEs	0.0	0.0	0.0	N/D	0.0	N/D
Discontinued Due to Clinical AEs	0.0	0.0	0.0	N/D	0.0	N/D
Patients Without Hepatitis B and/or C Co-Infection¶: Liver Function Tests						
Grade 3 or 4 ALT	1.5	1.9	3.6	2.4	3.0	2.9
Grade 3 or 4 AST	2.3	2.3	3.6	2.4	4.5	4.3
Grade 3 or 4 Total Bilirubin	0.8	0.0	3.6	2.4	2.0	1.9
Patients Without Hepatitis B and/or C Co-infection¶: Hepatobiliary Clinical Events						
All AEs	0.8	0.4	1.0	N/D	1.5	N/D
Drug-related§ AE	0.4	0.4	0.8	N/D	1.5	N/D
Serious AE	0.0	0.0	0.3	N/D	0.5	N/D
Discontinued Due to Clinical AE	0.0	0.0	0.3	N/D	0.0	N/D

TABLE 1. Selected Baseline Characteristics by Treatment Assignment for Participants in the Parent Study and DEXA Substudy

	All Treated Patients		Patients in the DEXA Substudy	
	Raltegravir Group (n = 281)	Efavirenz Group (n = 282)	Raltegravir Group (n = 55)*	Efavirenz Group (n = 57)*
Gender, n (%)				
Male	227 (81)	231 (82)	51 (93)	48 (84)
Female	54 (19)	51 (18)	4 (7)	9 (16)
Race/ethnicity, n (%)				
White	116 (41)	123 (44)	34 (62)	33 (58)
Black	33 (12)	23 (8)	14 (25)	9 (16)
Asian	36 (13)	32 (11)	0 (0)	1 (2)
Hispanic	60 (21)	67 (24)	5 (9)	11 (19)
Native American	1 (0.4)	1 (0.4)	0 (0)	1 (2)
Multiracial	35 (12)	36 (13)	2 (4)	2 (4)
Region, n (%)				
Latin America	99 (35)	97 (34)	—	—
South Asia	34 (12)	29 (10)	—	—
North America	82 (29)	90 (32)	55 (100)	57 (100)
Europe/Australia	66 (23)	66 (23)	—	—
Age, in yrs				
Mean (SD)	38 (9)	37 (10)	37 (9)	40 (10)
Median (min to max)	37 (19–67)	36 (19–71)	38 (20–61)	39 (21–67)
CD4 cell count, cell/mm^3				
Mean (SD)	219 (124)	217 (134)	236 (157)	226 (149)
Median (min to max)	212 (1–620)	204 (4–807)	231 (1–609)	202 (6–567)
Plasma HIV RNA, log 10 copies/mL				
Mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Median (min to max)	5.1 (3–6)	5.0 (4–6)	4.9 (4–6)	5.0 (4–6)
Investigator-reported history of AIDS				
Yes	52 (19)	59 (21)	10 (18)	8 (14)

TABLE 1. Selected Baseline Characteristics by Treatment Assignment for Participants in the Parent Study and DEXA Substudy

	All Treated Patients		Patients in the DEXA Substudy	
	Raltegravir Group (n = 281)	Efavirenz Group (n = 282)	Raltegravir Group (n = 55)*	Efavirenz Group (n = 57)*
Stratum, n (%)				
Screening HIV RNA level ≤50,000	75 (27)	80 (28)	16 (29)	15 (26)
Hepatitis B or C positive	18 (6)	16 (6)	2 (4)	4 (7)
Viral Subtype, n (%)				
Clade B	219 (78)	230 (82)	53 (96)	52 (91)
Non-Clade B	59 (21)	47 (17)	2 (4)	3 (5)
Missing	3 (1)	5 (2)	0 (0)	2 (4)
Baseline plasma HIV RNA, n (%)				
≤50,000 copies/mL	79 (28)	84 (30)	19 (35)	19 (33)
>50,000 copies/mL	202 (72)	198 (70)	36 (65)	38 (67)
≤100,000 copies/mL	127 (45)	139 (49)	31 (56)	27 (47)
>100,000 copies/mL	154 (55)	143 (51)	24 (44)	30 (53)
Baseline CD4 cell counts, n (%)				
≤50 cells/mm^3	27 (10)	31 (11)	8 (15)	9 (16)
>50 cells/mm^3 and ≤200 cells/mm^3	104 (37)	105 (37)	15 (27)	19 (33)
>200 cells/mm^3	150 (53)	145 (51)	32 (58)	29 (51)
Missing	0 (0)	1 (0.4)	0 (0)	0 (0)
Body mass at baseline				
Mean weight in kg (SD)	72 (15)	70 (16)	83 (15)	77 (23)
Mean BMI in kg/M^2 (SD)	24 (5)	24 (5)	27 (6)	25 (6)

*There were 111 patients with Dual Energy X-ray Absorptiometry (DEXA) scans at baseline: 86 patients were evaluable at Week 48 and 75 patients were evaluable Week 96, including 68 patients evaluable at both time points. One patient enrolled in the substudy from the efavirenz arm did not have a baseline scan and therefore was excluded from the DEXA analyses.

Dash indicates that only participants at US sites were eligible for the DEXA substudy.

n, number of patients; BMI, body mass index; SD, standard deviation.

TABLE 5. Frequency of Prespecified Grade 3/4* Laboratory Abnormalities†

Laboratory Test§	Toxicity Criteria†	Raltegravir Group N = 281, m/n (%)	Efavirenz Group N = 282, m/n (%)
Absolute neutrophil count	<750 cells/μL	7/281 (2.5)	3/278 (1.1)
Hemoglobin	<7.5 gm/dL	2/281 (0.7)	2/278 (0.7)
Platelet count	<50,000/μL	0/276 (0.0)	1/276 (0.4)
Fasting total cholesterol	>300 mg/dL	0/276 (0.0)	11/267 (4.1)
Fasting LDL-cholesterol	≥190 mg/dL	3/271 (1.1)	17/262 (6.5)
Fasting triglycerides	>750 mg/dL	1/276 (0.4)	4/267 (1.5)
Fasting glucose	>250 mg/dL	3/274 (1.1)	0/266 (0.0)
Total bilirubin	>2.5 × ULN	2/281 (0.7)	0/279 (0.0)
Alkaline phosphatase	>5 × ULN	0/281 (0.0)	2/279 (0.7)
Aspartate aminotransferase	>5 × ULN	9/281 (3.2)	8/279 (2.9)
Alanine aminotransferase	>5 × ULN	5/281 (1.8)	7/279 (2.5)

*Grades 3/4 by DAIDS criteria [http://rcc.tech-res-intl.com/tox_tables.htm].

†All treated patients were included in the safety analysis. All laboratory abnormalities exceeding the predefined limit of change through May 6, 2009 (the day when the last patient remaining in the study had their 96-week assessment) were tallied. Only patients with a worsened grade from baseline were included.

‡Although there were no grade 3 or 4 abnormalities of serum creatinine levels (≥1.9 × ULN), the frequency of grade 1 elevations in serum creatinine concentration from baseline was 5.7% (16 of 281) in the raltegravir group compared with 1.1% (3 of 279) in the efavirenz group, and the frequency of grade 2 elevations was 0.4% (1 of 281) in the raltegravir group compared with 0.4% (1 of 279) in the efavirenz group. The mean change from baseline was 0.01 for raltegravir recipients and −0.03 for efavirenz recipients.

N, total number of treated patients in each group.

m, number of patients with Grade 3 or 4 abnormalities of the specified laboratory test.

n, number of patients with results for the specified laboratory test.

ULN, upper limit of normal range.

Hepatic safety profile of raltegravir in HIV patients with chronic hepatitis C

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Background: ***Raltegravir*** (***RAL***) has shown good tolerability and safety in clinical trials,which generally have recruited HIV+ patients with not underlying serious conditions. HIV patients with chronic viral hepatitis represent a large group of patients in whom the tolerability of ***RAL*** has to be assessed.

Methods: A total of 311 antiretroviral-experienced HIV patients initiated ***RAL*** from Dec 2005 to Jan 2009 at our institution. Clinical data, laboratory parameters and liver stiffness (Fibroscan) were analyzed at baseline, month 1 and every 3 months. Hepatotoxicity was defined according to baseline ALT values. Any degree: >1.25-fold the upper limit of normality (31 IU/L) in patients with normal ALT and the baseline value in those with elevated ALT. For grade 3-4 hepatotoxicity, ALT increases >3.5-fold or >5-fold, respectively. HIV monoinfected and HIV/HCV co-infected (pos HCV-RNA) patients were compared.

Results: Data from 218 HIV patients were examined (126 HIV-mono and 92 HIV-HCV coinfected). Mean age 46±8 years; male 80%; median CD4 400 (22%)cells/μL; 64% plasma HIV-RNA< 50 copies/mL.

Any degree of hepatotoxicity developed in 10 (7.9%) HIV-mono and 23 (25%) coinfected patients ($p< 0.001$). Grade 3 or 4 hepatotoxicity was seen in only 3 patients, all co-infected. Occurred at months 1 (one) and 15 (two), in all other liver damage factors were involved. Multivariate analysis revealed HCV co-infection as the only independent variable associated with any degree of hepatotoxicity ($p=0.03$). The main reasons for ***RAL*** discontinuation were poor adherence (n=5), virological failure (n=3) and headache (n=1).

Conclusions: Elevations in liver enzymes are rarely seen in HIV patients treated with ***RAL***-containing regimens. They are uniformly mild and no cases of grade 3-4 hepatotoxicity could be attributed to ***RAL*** in our patients, 40% of whom were coinfected. The good hepatic safety profile of ***RAL*** should be added to its overall good tolerability. ***RAL*** may be an interesting option in HIV/HCV co-infected patients.