Hepatic safety profile of darunavir with low-dose ritonavir (DRV/r) in HIV/HCV coinfected and HIV monoinfected patients

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SUMMARY

The hepatic safety profile of ART including DRV/r was retrospectively evaluated in antiretroviral-experienced HIV-infected patients (18 HIV/HCV coinfected, group A and 29 infected with HIV alone, group B) during a 72 week study. During the study, liver enzyme values were higher in group A, but in the case of abnormal transaminase levels, the median values did not exceed 1.6xULN. This study showed evidence of long-lasting hepatic safety of ART including PI DRV/r in HIV/HCV coinfected and in HIV monoinfected persons.

KEY WORDS: Darunavir, Ritonavir, Liver toxicity, HIV, HCV

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Since their introduction, protease inhibitors (PIs) have been implicated in elevated liver enzymes in patients receiving ART (Aceti *et al.,* 2002; Meraviglia *et al.,* 2004). Concomitant HCV infection may be associated with a higher incidence of elevated liver enzymes (Sulkowski *et al.,* 2000; Savès *et al.,* 2000).

The duration of follow-up may also affect the incidence of hepatic enzyme flares. Albeit most drug-induced reactions occur within weeks to months of treatment initiation, delayed reactions occurring more than six months after therapy initiation have been reported (French *et al.,* 2004). Limited data (Rachlis *et al.,* 2007) are available concerning the effect of PI darunavir with low-dose ritonavir on hepatic enzymes in HIV/HCV coinfected individuals, with data of hepatic safety profile recorded during a short follow-up period. To assess the safety of ART including DRV/r on the liver tests, liver enzyme values were measured during 72 weeks (72W) ART including DRV/r in HIV monoinfected and HIV/HCV double infected individuals. A retrospective study exploring the hepatic safety profile of ART including DRV/r 600 mg/100 mg bid was conducted in 47 antiretroviral-experienced HIV-infected patients (18 individuals HIV/HCV coinfected, group A and 29 individuals with HIV alone, group B) from January 2006 to July 2007 at a reference HIV clinic. Standard laboratory assessment including liver enzymes, $CD4^+$ cell counts and HIV load were collected at baseline, (at DRV/r based ART initiation) and every 12 weeks thereafter for 72 weeks. The diagnosis of chronic hepatitis in HIV/HCV coinfected individuals was performed via clinical/biochemical/ultrasonographic evaluation and transient elastography.

Among 18 individuals with HCV-related chronic hepatitis, three cases showed evidence of cirrhosis. Liver enzymes were monitored using the upper limit of normal for alanine aminotransferase (ALT, ULN= 55 U/L); aspartate aminotransferase (AST, ULN=41 U/L); gamma glutamyl transferase (GGT, ULN=50 U/L); total bilirubin, (TB, ULN=1.0 mg/dL). The change in serum ALT and

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AST from pre-treatment levels to the highest levels during treatment were also categorized according to the ACTG grading scale (AIDS Clinical Trials Group, 1992). Based on the scale, ALT, AST levels were classified as grade 1 (1.25-2.5 ULN; grade 2 (>2.5-5.0 x ULN); grade 3, (>5-10.0 x ULN); or grade 4 (>10 x ULN). Similarly, hyperbilirubinemia was classified as grade 1 (1.1-1.5 x ULN) grade 2 (1.6-2.5 x ULN), grade 3 (2.6-5.0 x ULN), grade 4 (>5.0 x ULN).

Patients with elevated pretreatment serum ALT and AST levels (>ULN) were classified based on changes relative to the baseline value rather than to the ULN: grade 0 (<1.25 x baseline); grade 1, (1.25-2.5 x baseline); grade 2, (2.6-3.5 x baseline); grade 3, (3.6-5 x baseline); grade 4 (>5 x baseline) according to a modified standardized toxicity grade scale (Sulkowski *et al.,* 2004). If the ALT and AST grades were discordant, the higher of the two grades was used for classification. Demographic and clinical characteristics were compared for group A and B using χ^2 tests for categorical variables and Mann-Whitney tests for continuous variables. Data are reported as median and inter-quartile range (IQR) when appropriate. *P* values <0.05 were considered statistically significant. All of the study participants gave their informed consent.

Characteristic of patients at baseline are summarized in Table 1. The majority of individuals were males in both groups. Age at initiation of DRV/r based ART was similar between groups A and B. At diagnosis of HIV infection, patients of group B were older than those of group A; however, HIV/HCV coinfected individuals had a longer duration of HIV infection.

The mode of HIV transmission differed between the two groups: patients of group A prevalently acquired HIV infection by intravenous drug use (IVDU), while those of group B more frequently acquired HIV infection by the sexual route. At baseline, the two groups showed similar $CD4^+$ cells count and HIV-RNA levels; median ALT, GGT and TB levels were within normal range in

TABLE 1 - *Baseline characteristics of HIV/HCV (group A) coinfected and HIV (group B) infected individuals under ART including DRV/r*

	Group A	*Group B*	*P-value*
No. patients	18	29	
Males (%)	16 (89)	24 (83)	
Age, years*	44 (43-45)	46 (41-52)	0.24
Age at HIV infection, years*	24 (23-29)	31 (26-34)	0.003
Years since HIV infection*	20 (16-22)	15 (14-18)	0.0025
Risk factor for HIV transmission (%)			
Sexual	2 (11)	19 (65)	<0.0001
IVDU†	14 (78)	1 (3)	
Unknown	2 (11)	9 (31)	
$CD4^+$ T cells number (cells/mm^3)*	205 (52-270)	205 (54-264)	0.835
HIV-RNA (Log copies/mL)*	4.6 (3.7-4.9)	4.6 (3.2-5.0)	0.5
AST (U/L)*	44 (23-75)	31 (23-40)	0.201
ALT (U/L)*	50 (20-79)	33 (20-48)	0.201
GGT (U/L)*	37 (29-56)	34 (28-76)	0.277
Total bilirubin (mg/dL)*	0.5 (0.4-0.9)	0.5 (0.4-0.9)	0.601
Antiretrovirals used along with DRV/r			
NRTIs (%)	16 (89)	25 (86)	
NNRTIs (%)	3 (17)	7 (24)	
Enfuvirtide (FI, %)	4 (22)	8 (28)	

*Median and inter-quartile range; †IVDU=intravenous drug users.

both groups, while AST levels were above the ULN in group A, but no difference in liver test values was observed between the two groups. Previous drug exposure was well-balanced between the two groups.

Eighty-nine percent of patients in group A and 93% in group B received a nucleoside and/or nucleotide reverse transcriptase inhibitor (NRTI); 17% group A patients and 21% group B experienced a non-nucleoside reverse transcriptase inhibitor (NNRTI); 83% of group A and 76% of group B were under ART including PIs. Finally, one patient in group A and two in group B experienced a fusion inhibitor (FI) enfuvirtide. Treatment schedules at baseline were similar between the two groups (Table 1).

Liver function tests and $CD4^+$ cells count throughout the 72 week study are summarized in Figure 1. $CD4^+$ cells count and HIV-RNA load were similar in groups A and B. HIV-RNA was detectable at baseline (Table 1) and W12 in both groups: W12 median value, 1.84 Log copies/mL; IQR 1.69-2.33, in group A and median value, 1.81 Log copies/mL, IQR 1.69-2.03 in group B; p=0.832,

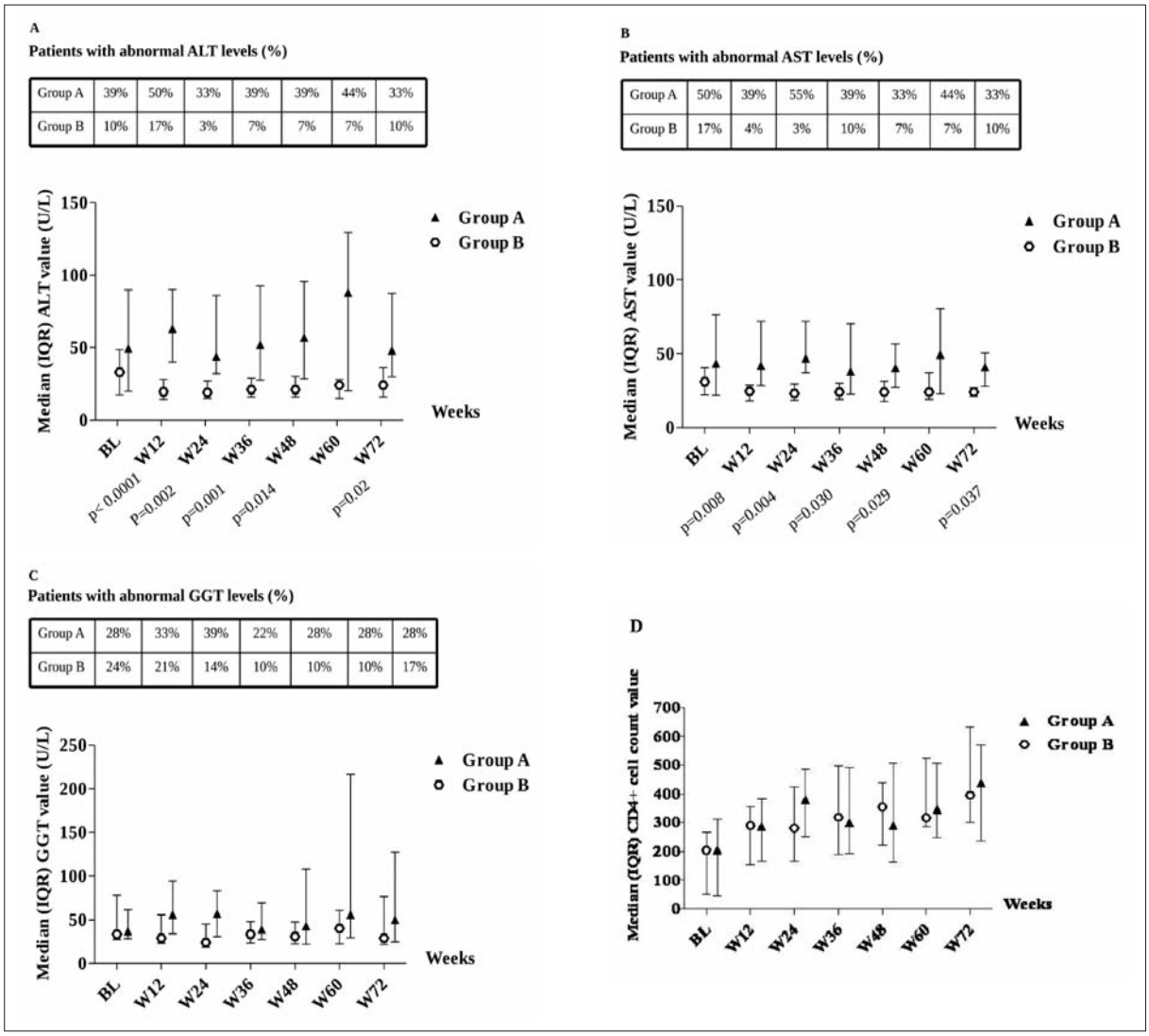

FIGURE 1 - *Evaluation of ALT (A); AST (B); GGT (C) levels and CD4+ (D) cell count at different time points during the 72 week study. Significant P values were reported for each time point. The percentage of patients with abnormal liver enzyme levels is listed.*

and below the detection limit of the assay (<1.69 Log copies/mL) in the remaining time points in both groups.
During the 72 week study, median ALT and AST values were invariably higher in HIV/HCV coinfected with respect to HIV monoinfected individuals at each time point, except W60, where the difference was not statistically significant. In the case of abnormal transaminases (ALT and/or AST) in group A, the median values did not exceed 1.6 x ULN (grade 1 liver toxicity). Median GGT values were higher in group A than group B, but GGT levels did not reach a significant difference at any time point.
Median TB levels remained within the normal value during the follow-up period. A higher rate of abnormal liver enzymes at baseline and during treatment were observed in individuals of group A vs. those of group B (Figure 1).
None of individuals with abnormal liver enzymes at baseline showed a worst of liver function tests >1 x baseline, according to a standardized modified scale. One of three individuals with cirrhosis had normal transaminase levels at baseline that were maintained during the 72 week follow-up. Of the other two individuals with cirrhosis, one had ALT and AST levels 2.0 x ULN at baseline and during the follow-up.
The remaining patient had ALT levels 2.0 x ULN and AST value 1.5 x ULN at baseline, that were maintained at the same levels during the follow-up. At baseline, before initiation of DRV/r based ART, one patient in group A had severe transaminases elevation, (grade 3 liver toxicity) due to acute hepatitis A, that resolved at W12 follow-up, and one other patient in group B had a mild transaminases increase (grade 2 liver toxicity) that returned to normal values at W12 evaluation.

DISCUSSION

HIV/HCV coinfected people are considered at higher risk of liver toxicity, but the causal association between a specific drug and liver enzymes increase is difficult to determine in this setting, also because in the majority of cases drug-induced liver injury can range from mild to asymptomatic elevation.
Albeit ART and HCV seem to interact synergically to increase the possibility of transaminases elevation, the mechanism by which HCV may lead to higher risk for elevated liver enzymes is unclear.
Evidence (Puoti *et al.*, 2003) suggests that chronic HCV infection is the driving force behind liver test abnormalities. So, intrinsic liver disease consequent to chronic hepatitis C may increase the risk of elevated liver enzyme values. Treatment with PI is associated with an increased risk for transaminases elevation, but little is known (Katlama *et al.*, 2007) on liver function tests during treatment including DRV/r in HIV/HCV coinfected persons. In this regard, Rachlis *et al.* evaluated liver safety parameters of DRV/r in Power 1 and 3 trials during a short follow-up period of 24 weeks.
The present study evaluated liver enzymes safety profile in HIV/HCV coinfected individuals followed during 1.5 years of DRV/r-based ART. Albeit HIV/HCV coinfected individuals showed transaminase levels higher than those with single HIV infection, none of them discontinued ART or had a rechallenge of ART. These patients were receiving a stable treatment before changing to an ART including DRV/r, and NRTI or NNRTI drugs were similarly distributed in the two groups before and after initiating a DRV/r-based ART.
Of note, patients of group B prevalently acquired HIV infection through sexual contact, had a shorter period of HIV infection and probably a shorter period of HIV medication. Conversely, HIV/HCV coinfected patients were more frequently IVDU and had a longer period of HIV infection; so, apart of HCV-related liver disease, concomitant or previous illicit drugs use and longer period of HIV medication may have contributed to liver damage in this setting. Unfortunately, alcohol intake was not systematically recorded.
Therefore, an important factor associated with liver damage was not explored.
In conclusion, this study, albeit performed in a small group of patients, showed that ART including PI DRV/r is sufficiently safe during 72 weeks follow-up in HIV/HCV coinfected and in HIV monoinfected persons. Therefore, standard clinical monitoring should be considered adequate in HIV/HCV coinfected patients receiving DRV/r based ART treatment.

REFERENCES

ACETI A., PASQUAZZI C., ZECHINI B., DE BAC C. LIVERHAART GROUP. (2002). Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. *J. Acquir. Immune Defic. Syndr*. **29**, 41-48.

AIDS CLINICAL TRIALS GROUP. Division of AIDS table for grading severity of adult adverse experiences-August 1992. Available at: http://rcc.techres.com/DAIDS%20RCC%Forms/ToxicityTable Adult_TRP_v01a.pdf. Accessed, May, 8, 2010.

FRENCH A.L., BENNING L., ANASTOS K., AUGENBRAUN M., NOWICKI M., SATHASIVAM K., TERRAULT N.A. (2004). Longitudinal effect of antiretroviral therapy on markers of hepatic toxicity: impact of hepatitis C coinfection. *Clin. Infect. Dis*. **39**, 402-410.

KATLAMA C., ESPOSITO R., GATELL J.M., GOFFARD J.C., GRINSZTEJN B., POZNIAK A., ROCKSTROH J., STOEHR A., VETTER N., YENI P., PARYS W., VANGENEUGDEN T.; POWER 1 STUDY GROUP. (2007). Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-week results of POWER 1. *AIDS*. **21**, 395-402.

MERAVIGLIA P., SCHIAVINI M., CASTAGNA A., VIGANÒ P., BINI T., LANDONIO S., DANISE A., MOIOLI M.C., ANGELI E., BONGIOVANNI M., HASSON H., DUCA P., CARGNEL A. (2004). Lopinavir/ritonavir treatment in HIV antiretroviral-experienced patients: evaluation of risk factors for liver enzyme elevation. *HIV Med*. **5**, 334-343.

PUOTI M., TORTI C., RIPAMONTI D., CASTELLI F., ZALTRON S., ZANINI B., SPINETTI A., PUTZOLU V., CASARI S., TOMASONI L., QUIROS-ROLDAN E., FAVRET M., BERCHICH L., GRIGOLATO P., CALLEA F., CAROSI G.; HIV-HCV CO-INFECTION STUDY GROUP. (2003). Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. *J. Acquir. Immune Defic. Syndr.* **32**, 259-267.

RACHLIS A., CLOTET B., BAXTER J., MURPHY R., LEFEBVRE E. (2007). Safety, tolerability, and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced, hepatitis B or C co-infected patients in POWER 1 and 3. *HIV. Clin. Trials*. **8**, 213-220.

SAVÈS M., RAFFI F., CLEVENBERGH P., MARCHOU B., WALDNER-COMBERNOUX A., MORLAT P., LE MOING V., RIVIÈRE C., CHÊNE G., LEPORT C. (2000). Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob. Agents. Chemother.* **44**, 3451-3455.

SULKOWSKI M.S., THOMAS D.L., CHAISSON R.E., MOORE R.D. (a 2000). Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* **283**, 74-80.

SULKOWSKI M.S., MEHTA S.H., CHAISSON R.E., THOMAS D.L., MOORE R.D. (b 2004). Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS.* **18**, 2277-2284.