NEW MICROBIOLOGICA, **30**, 279-282, 2007

Liver function parameters in HIV/HCV co-infected patients treated with amprenavir and ritonavir and correlation with plasma levels

Vincenzo Spagnuolo[1], Gianluca Gentilini[2], Anna De Bona[1], Laura Galli[1], Caterina Uberti-Foppa[1], Armando Soldarini[2], Fernanda Dorigatti[2], Elena Seminari[1]

[1]Infectious Disease Department, San Raffaele Scientific Institute and Università Vita-Salute San Raffaele Milan, Italy; [2]Laboraf, San Raffaele Scientific Institute and Università Vita-Salute San Raffaele Milan, Italy

SUMMARY

Acute liver toxicity is a frequent adverse event that occurs during antiretroviral therapy and was observed in 6-30% of the patients on treatment, especially in presence of HCV coinfection (Cooper *et al.*, 2002, Maida *et al.*, 2006, Sulkowski *et al.*, 2000). A correlation between HCV-associated liver-fibrosis severity and the risk of HAART associated hepatoxicity has been demonstrated (Aranzabal *et al.*, 2005, Sulkowski *et al.*, 2004). This high liver toxicity rate might be due to increased drug exposure in patients with liver disease (Veronese *et al.*, 2000). It has been reported that patients with chronic hepatitis C show significantly reduced CPY3A4 and CYP2D6 activity in comparison with healthy volunteers (Becquemont *et al.*, 2002). The aim of this study was to evaluate the liver function tests in HCV-co-infected patients treated with fos-amprenavir and ritonavir.

KEY WORDS: Cirrhosis, Fos-amprenavir, HCV-infection

Patients included in this study received a single boosted PI based regimen containing fos-amprenavir/ritonavir (700/100 mg bid). The patients were divided into groups with different liver impairment:

1) HIV-infected patients with chronic hepatitis (documented by detectable plasma HCV-RNA/HBV-DNA and liver histology);
2) HIV-infected patients with liver cirrhosis (documented by CT scan, ultrasound and/or liver histology); and
3) patients with normal liver function test results, and without history of HCV or HBV co-infection (control group).

The patients with liver impairment were eligible for the study if at baseline they had not signs and symptoms of acute liver decompensation such as encephalopathy, severe ascites, bleeding from esophageal varices.

Liver function parameters evaluated were: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total and direct bilirubin, cholinesterases (CHE), albumin, platelet count.

Liver function parameters were evaluated at baseline, and, successively, at week 4, 12, and 24 on therapy.

Amprenavir and ritonavir plasma levels were determined by High Pressure Liquid Cromatography. Pharmacokinetic calculations on plasma amprenavir and ritonavir concentrations were performed using WinNonlin 4.1.

Wilcoxon's signed rank test was applied within each group to assess significant variations in liver function variables from baseline to weeks 4, 12 and 24. Friedman analysis was applied to evaluate variation in degree of liver function test

Corresponding author
Vincenzo Spagnuolo
Infectious Disease Department
Via Stamira d'Ancona 20
20122 Milan, Italy
E-mail: vincenzo.spagnuolo@tiscali.it

along the 24-week follow-up among the groups. To assess linear correlation between the pharmacokinetics and the liver function parameters, the Spearman rank correlation coefficient was estimated.

All of the statistical tests were two-sided at the 5% level, and performed using SAS Software, release 8.2.

The study involved 21 HIV-infected patients: seven with chronic hepatitis (6 HCV infected and 1 with HBV-HCV co-infection) as staged by liver biopsy, eight with liver cirrhosis (7 with HCV and 1 with HBV-HCV co-infection), and six controls. Age in the three groups was comparable (group 1: 43 (39-49) years, group 2: 44 (39-50) years, group 3: 42 (35-55) years), as well as weight (group 1: 68 (58-78) Kg, group 2: 68 (55-85) Kg, group 3: 70 (52-86) Kg). Lymphocytes CD4+ were respectively: 317 (104-1041) cell/µL, 197 (40-629) cell/µL, 483 (269-1042) cell/µL. HIV-RNA was respectively: 57 copies/mL, 218 copies/mL, <50 copies/mL.

Median amprenavir AUC_{0-12} value in control group was 41237 (15292-53176) ng.h/ml and C_{max} was 5581 (2105-8255) ng/ml, in chronic hepatitis group AUC_{0-12} was 39767 (26448-96599) ng.h/ml, GMR (95% CI) = 1.24 (1.10-1.39); C_{max} was 5325 (4170-14182) ng/ml, GMR (95% CI) = 1,20 (1,03-1,40); in cirrhosis group AUC_{0-12} was 53957 (38586-86823) ng.h/ml, GMR (95% CI) = 1.64 (1.25-2.14); C_{max} was 8430 (5386-10048) ng/ml, GMR (95% CI) = 2.00 (1.80-2.22). Amprenavir AUC_{0-12} and C_{max} were 50-60% higher in the cirrhotic group than in the controls; the patients with chronic hepatitis showed a significant (roughly 20%) increase in AUC_{0-12} and C_{max} in comparison with controls.

Median ritonavir AUC_{0-12} value in control group was 6384 (2417-12427) ng.h/ml and C_{max} was 1019 (389-1852) ng/ml; in chronic hepatitis group AUC_{0-12} was 5903 (4552-6897) ng.h/ml, GMR (95% CI)= 1.00 (0.59-1.69), C_{max} was 828 (744-1807) ng/ml, GMR (95% CI)= 1.4 (0.72-1.81); in cirrhosis group AUC_{0-12} was 9681 (2845-22259) ng.h/ml, GMR (95% CI) = 1.52 (1.47-1.58), C_{max} was 1350 (458-3612) ng/ml, GMR (95% CI) = 1.54 (1.45-1.64). In comparison with the controls, the cirrhotic patients had higher ritonavir AUC_{0-12} and C_{max}, whereas the concentration time profiles overlapped in the chronic hepatitis and con-

TABLE 1 - *Liver function parameters at baseline and at weeks 4, 12 and 24.*

		Baseline	*Week4*	*Week12*	*Week24*
ALT (UI/L)	Chronic hepatitis	157 (38-226)	146 (46-248)	101 (42-267)	155 (59-170)
	Cirrhosis	97 (42.5-171.5)	110.5 (62-161)	86 (73-88)	69 (35-119)
	Controls	49 (45-52)	24 (22-35)	20.5 (18.5-36.5)	23 (19-39)
AST (U/L)	Chronic hepatitis	119 (49-160)	112 (46-164)	93 (46-175)	119 (66-161)
	Cirrhosis	123 (85.5-190.5)	129 (94-209)	90 (78-144)	81.5 (48-101)
	Controls	39 (37-42)	26 (22-31)	24.5 (23-30)	24 (21-24)
Bili. Tot. (mg/dL)	Chronic hepatitis	0.63 (0.6-0.9)	0.58 (0.39-0.7)	0.54 (0.42-0.78)	0.82 (0.6-0.83)
	Cirrhosis	1.46 (1.-3.4)	1.46 (1.2-3.86)	1.83 (1.7-2.7)	1.54 (1.22-1.95)
	Controls	0.48 (0.31-0.59)	0.52 (0.45-0.59)	0.61 (0.45-0.69)	0.45 (0.39-0.58)
Bili Dir. (mg/dL)	Chronic hepatitis	0.24 (0.18-0.26)	0.24 (0.18-0.26)	0.20 (0.12-0.35)	0.22 (0.21-0.27)
	Cirrhosis	0.69 (0.48-1.94)	0.71 (0.51-2.29)	0.98 (0.64-1.25)	0.66 (0.48-0.92)
	Controls	0.16 (0.11-0.25)	0.16 (0.14-0.18)	0.13 (0.09-0.17)	0.11 (0.10-0.15)
ALP (U/L)	Chronic hepatitis	222.5 (168-280)	203 (202-204)	223.5 (185-281)	265 (209-315)
	Cirrhosis	421 (390-482)	425 (343-547)	482 (414-534)	359 (335-614)
	Controls	209 (203-214)	187 (169-368)	195 (185-226)	267 (186-271)
GGT (U/L)	Chronic hepatitis	122 (62-247)	268 (86-334)	110 (81-301)	161 (127-208)
	Cirrhosis	91.5 (69-194)	77 (65-220)	65 (63-102)	86.5 (52-97)
	Controls	41 (29-59)	29 (29-36)	36 (25.5-104.5)	55 (36-64)

AST = aspartate aminotransferase, ALT= alanine aminotransferase, ALP= alkaline phosphatase, GGT= gamma glutariltransferase.

trol groups. Liver function parameters (AST, ALT, total bilirubin, direct bilirubin, GGT and alkaline phosfatase) measured at weeks 4, 12 and 24 are reported in table 1. Within each group, no significant correlations between amprenavir and ritonavir $AUC_{0\text{-}12}$ and AST, ALT, ALP, CHE, albumin, platelets values on the day of pharmacokinetic analysis were observed. No variation over time of liver parameters was observed among the 3 groups (p=0.96) (Figure 1). Among all patients, a significant correlation was observed between amprenavir $AUC_{0\text{-}12}$ and total bilirubin values (r=0.64, p=0.003). Liver function parameters in patients treated with fos-amprenavir and ritonavir did not worsened during time. Cohort studies have shown that highly active antiretroviral therapy (HAART) can improve liver-related mortality in HIV/hepatitis C virus (HCV)-coinfected patients. A reduction in the accelerated liver fibrosis progression observed in HIV

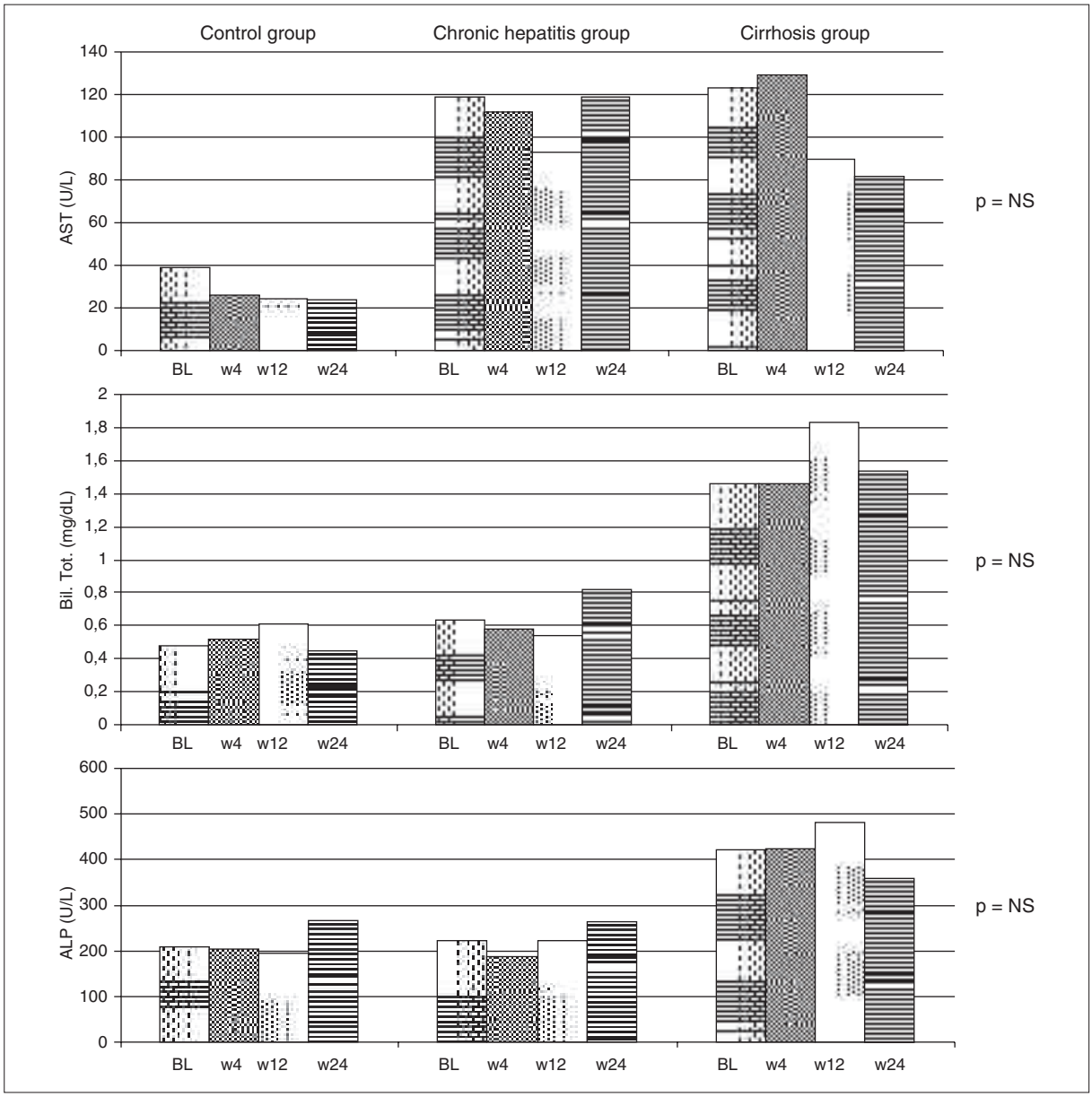

FIGURE 1 - *Variation over time of liver function parameters.*

infection induced by HAART could explain these findings. The use of PI-based HAART in HIV/HCV-coinfected patients seems to be associated with less severe fibrosis and slower progression of fibrosis (Macías *et al.*, 2006).

Cirrhotic patients had increased plasma amprenavir levels and also the patients within chronic hepatitis group had higher AUC_{0-12} and C_{max} values. In a recent paper, lopinavir and ritonavir exposure was analysed in HIV-infected patients with or without HCV co-infection, and it was not observed a difference in lopinavir plasma concentration between different groups. However, ritonavir exposure may be higher in this setting, particularly in individuals with advanced liver fibrosis (Moltó *et al.*, 2007).

Despite HCV infection is associated to increased risk of liver toxicity due to HAART, the survival of HIV/HCV-co-infected patients with end stage liver disease is extremely poor, HAART seems to be associated with a reduced liver-related mortality (Merchante *et al.*, 2006).

The clinical significance of the increased plasma levels of protease inhibitors in patients with chronic hepatitis or cirrhosis is still a matter of debate. HBV or HCV coinfection is a risk factor for developing hepatotoxicity during HAART (Mocroft *et al.*, 2005, Mouly *et al.*, 2006), but no association has been found between the plasma levels of some protease inhibitors (lopinavir and ritonavir) and the development of hepatoxicity (Canta *et al.*, 2005). In our study we did not observe a worsening of hepatic parameters in patients with HCV co-infection, compared to patients without HCV co-infection, despite increased plasma levels. Additional studies that analyze other factors possibly correlated to drug-induced liver injury (i.e. alcohol or illicit drug intake, concomitant diseases, diet) are needed.

ACKNOWLEDGMENTS

We would like to thank San Raffaele's Infectious Diseases Department, Laboraf HSR and a special thanks to our patients.

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