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Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy

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SUMMARY. The recent availability of non-invasive tools to measure liver fibrosis has allowed examination of its extent and determination of predictors in all patients with chronic hepatitis C virus (HCV) infection. On the other hand, most information on hepatic fibrosis in HCV/human immunodeficiency virus (HIV)-coinfected patients has been derived from liver biopsies taken before highly active antiretroviral therapy (HAART) was widely available. All consecutive HCV patients with elevated aminotransferases seen during the last 3 years were evaluated and liver fibrosis measured using transient elastography (FibroScan®) and biochemical indexes. Patients were split according to their HIV serostatus. A total of 656 (69.6%) HCV-monoinfected and 287 (30.4%) HIV/HCV-coinfected patients were assessed. Mean CD4 count of coinfected patients was 493 cells/μL and 88% were under HAART (mean time, 4.2 ± 2.4 years). Advanced liver fibrosis or cirrhosis was recognized in 39% of the coinfected and 18% of the monoinfected patients ($P < 0.005$). A good correlation was found between FibroScan® and biochemical indexes [AST to platelet ratio index ($r = 0.405$, $P < 0.0001$), FIB-4 ($r = 0.393$, $P < 0.0001$) and Forns ($r = 0.407$, $P < 0.0001$)], regardless of the HIV status. In the multivariate analysis, age >45 years, body mass index (BMI) >25 kg/m^2, and HIV infection were independently associated with advanced liver fibrosis or cirrhosis. HIV/HCV-coinfected patients have more advanced liver fibrosis than HCV-monoinfected patients despite the immunologic benefit of HAART.

Keywords: coinfection, FibroScan, hepatitis C, HIV, liver fibrosis, transient elastography.

INTRODUCTION

Before the advent of highly active antiretroviral therapy (HAART), most deaths in HIV-infected patients were on account of acquired immunodeficiency syndrome (AIDS)-related illnesses. The improved life expectancy of HIV-infected persons receiving HAART has permitted those complications on account of other concurrent diseases to become manifest. In this regard, no doubt chronic hepatitis C virus (HCV) coinfection has attracted considerable attention within the last few years. Progressive hepatic fibrosis, up to the development of cirrhosis, is a feature of almost all chronic liver diseases. HIV-coinfection accelerates the progression of HCV-related fibrosis, particularly in patients with elevated alcohol consumption and/or severe immune suppression [1,2]. A growing number of deaths in HIV-infected persons are currently on account of complications of end-stage liver disease secondary to chronic hepatitis C, including the development of hepatocellular carcinoma [3–5]. Fortunately, HIV/HCV-coinfected patients under effective HAART seem to benefit from slower liver fibrosis progression compared with patients with uncontrolled HIV disease [6,7]. However, this assessment has been derived from a selected group of patients, as those who accepted a liver biopsy in the

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus.

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workup for interferon-based therapies, and therefore may not apply to all HIV/HCV-coinfected patients. Moreover, it is unclear whether long-term exposure to HAART may enhance liver fibrosis by other mechanisms, including hepatic steatosis, and whether the expected benefit of HAART on HCV-related liver fibrosis throughout immune recovery may be blunted.

Liver biopsy is considered the 'gold standard' for assessing hepatic fibrosis. However, this is an invasive and potentially life-threatening procedure [8,9] and its accuracy in assessing hepatic fibrosis has been questioned because of sampling error and inter-observer variability. Of note, histologic understaging is particularly common in patients with compensated cirrhosis [10,11]. For all these reasons, non-invasive tools to measure liver fibrosis have been developed and are entering rapidly into the clinical practice. They are mainly represented by serum fibrosis markers and imaging techniques. Among the latest, transient elastography (FibroScan®, Echosens, Paris, France) is a rapid tool that reliably measures liver stiffness by means of wave emission. The correlation between the extent of hepatic fibrosis assessed both by histology and FibroScan® has proven to be relatively good in patients with chronic hepatitis C, regardless of the HIV infection [12–14].

The aim of this study was to assess the prevalence of advanced liver fibrosis and cirrhosis using transient elastography and biochemical markers in a large group of patients with chronic hepatitis C seen within the last 3 years at two large European clinics, and to identify such of those factors that are associated with the severity of liver damage.

PATIENTS AND METHODS

Study population

Between January 2004 and April 2006, all consecutive patients with chronic hepatitis C seen at two large hospitals in Spain (Hospital Carlos III, Madrid) and France (Centre Hôpitalier Universitaire, Bordeaux), both with and without HIV coinfection, underwent liver fibrosis assessment using FibroScan®. For the purpose of this study, only individuals with detectable serum HCV-RNA and elevated alanine aminotransferases were included. Patients with acute liver decompensation, hepatocellular carcinoma, prior interferon exposure, current alcohol intake of more than 30 g/day, chronic hepatitis B, and autoimmune or genetic liver diseases were excluded. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients were enrolled after written informed consent was obtained.

Clinical and virological data collection

Information on risk factors for HCV and HIV infections, estimated duration of HCV infection, and antiretroviral treatment in HIV-positive patients were all recorded in a database specially designed for this study. Time of infection was estimated only for patients with a past history of transfusion or intravenous drug use. For all patients, HCV genotype and plasma HCV-RNA levels were recorded. In HIV-infected patients, CD4+ T-cell counts and plasma HIV-RNA levels were also recorded.

Liver fibrosis estimates

All patients underwent liver stiffness measurement using FibroScan®. Details on the technique and examination procedure have been reported elsewhere [15]. Briefly, the tip of the probe transducer was placed on the intercostal spaces at the level of the right lobe of the liver. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. The measurement depth was between 25 and 65 mm below the skin surface. At least five successful measurements were performed on each patient, with a ratio of the number of successful measurements to the total number of acquisitions not below 30%. The results are expressed in kilopascal (kPa) units. The median value of all acquisitions was deemed as representative of the liver elasticity for each patient. Advanced liver fibrosis (severe fibrosis and cirrhosis) was defined as a median liver stiffness ≥9.5 kPa. As previously published, this cut-off value is strongly correlated with a Metavir score ≥F3, both in HCV-monoinfected and HCV/HIV-coinfected patients [12–14].

Estimates of hepatic fibrosis were also made using three different biochemical indexes. The APRI index was calculated as follows: aspartate aminotransferase (AST)/upper limit of normal (ULN) × 100/platelet count (10^9/L) [16]. The FIB-4 index was calculated as follows: age ([age] × AST [IU/L]/[(platelet count [10^9/L]) × (ALT [IU/L])$^{1/2}$] [17]. Finally, the Forns index was calculated as follows: $7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{age}) - 0.014 \times (\text{cholesterol})$ [18].

Statistical analysis

Results are expressed as mean ± standard deviation or median (range) when high variability was found, and significance was set up for *P*-values below 0.05. Qualitative data were compared using the chi-squared test. Comparisons of quantitative data were made using the Student's *t*-test or the non-parametric Mann–Whitney rank-sum test when data did not exhibit a normal distribution. Kendall's coefficients of correlation (tau-b) and their associated probabilities (*P*) were used to evaluate the relationship between parameters. The odds ratio, together with its 95% confidence interval (CI) and the corresponding *P*-value were calculated for assessment of relative risks using logistic regression. Multivariate analysis was performed including all variables statistically associated in the univariate analysis ($P < 0.05$) and biologically related with the progression of liver fibrosis.

Statistical analyses were performed with SPSS 14.0 Statistical Software (SPSS Inc, Chicago, IL, USA).

RESULTS

Study population

A total of 943 patients were enrolled in the study. Their characteristics at the time of liver stiffness measurement, according to their HIV serostatus, are summarized in Table 1. There were 656 (69.6%) HCV-monoinfected patients and 287 (30.4%) HIV/HCV-coinfected patients. Coinfected patients were significantly younger than monoinfected individuals (43 *vs* 53 years). The most frequent HCV risk factor was intravenous drug use in coinfected patients (83%), while it was transfusion of blood products in monoinfected patients (45%). Most HIV-positive patients (87.8%) were under HAART, for a mean time of 4.2 ± 2.4 years. Of note, HIV/HCV-coinfected patients were more often infected by HCV genotype 3 (22%) when compared with HCV-monoinfected patients (9%).

Extent of liver fibrosis

Liver stiffness measurements by FibroScan ranged from 2.5 to 70.6 kPa (median: 6.3 kPa) in the overall population. Values for transient elastography as well as for serum fibrosis markers are recorded in Table 2. Overall, HCV-monoinfected patients had either absence of or mild fibrosis (F0–F1) more frequently (69%), while HIV/HCV-coinfected patients had more often (38.9%) severe fibrosis (F3) or cirrhosis (F4). The prevalence of severe fibrosis or cirrhosis estimated using as reference a FIB-4 index >3.25 was 10.9% and 22% in monoinfected and coinfected patients, respectively ($P < 0.001$).

In the whole group, a strong correlation was found between FibroScan® values and APRI ($r = 0.405$, $P < 0.0001$), FIB-4 ($r = 0.393$, $P < 0.0001$) and Forns ($r = 0.407$, $P < 0.0001$) indexes. Of note, FibroScan® values also correlated with aminotransferase levels ($r = 0.284$, $P < 0.0001$ for AST, and $r = 0.397$, $P < 0.0001$ for ALT). The correlation between FibroScan® and serum biomarkers indexes was highly significant both in

Table 1 Main characteristics of the study population according to HIV serostatus

	HCV patients ($n = 656$)	HCV/HIV patients ($n = 287$)	P
Age (years)	52.8 ± 14.5	42.9 ± 5.8	<0.0001
Male gender (%)	252 (38.4)	192 (66.9)	<0.0001
Body mass index (kg/m^2)	23.9 ± 3.7	21.4 ± 3.5	<0.0001
Mode of contamination	495	169	<0.0001*
Transfusion	222 (44.8)	11 (6.5)	
Intravenous drug use	105 (21.2)	140 (82.8)	
Others	168 (34.0)	18 (10.7)	
Mean age at contamination (years)	29.0 ± 14.2	20.0 ± 4.7	<0.0001
Mean duration of HCV infection (years)	23.5 ± 7.9	22.1 ± 5.9	0.04
Median AST (IU/L) (range)	40 (16–420)	67 (18–437)	<0.0001
Median ALT (IU/L) (range)	59 (10–535)	79 (16–495)	<0.0001
Median GGT (IU/L) (range)	40 (9–541)	87 (13–1308)	<0.0001
Mean platelet count (10^9/L)	236 ± 73	181 ± 72	<0.0001
Mean prothrombin time (%)	92.1 ± 12.0	92.4 ± 14.2	NS
HCV genotype (%)	656	219	<0.0001†
1	396 (60.4)	136 (62.1)	
2	132 (20.1)	7 (3.2)	
3	58 (8.8)	48 (21.9)	
4	62 (9.5)	28 (12.8)	
5 & 6	8 (1.2)	0 (0)	
Median HCV-RNA (IU/L) (range)	676 000 (615–3 330 000)	2 160 000 (2000–47 300 000)	<0.0001
Mean HIV-RNA (IU/L)		62 778 ± 726 625	
Mean CD4+ count (cells/μL)		492.8 ± 268.3	
HAART treatment (%)		252 (87.8)	

*Intravenous drug users *vs* others.
†For genotypes 2 and 3.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; HAART, highly active antiretroviral therapy; NS, not significant.

Table 2 Estimates of liver fibrosis using non-invasive tools in patients with chronic hepatitis C according to HIV serostatus

	HCV patients (n = 656)	HCV/HIV patients (n = 287)	P
Mean liver stiffness in kPa*	7.7 ± 6.4	12.0 ± 10.9	<0.0001
<7.1 (F0–F1)	453 (69.0)	114 (39.7)	<0.0001
7.1 to 9.4 (F2)	88 (13.4)	61 (21.3)	0.002
9.5 to 12.4 (F3)	47 (7.2)	34 (11.8)	0.02
≥12.5 (F4)	68 (10.4)	78 (27.1)	<0.0001
Mean APRI score	0.76 ± 1.04	1.20 ± 1.19	<0.0001
Median APRI score (range)	0.44 (0.13–9.29)	0.78 (0.16–6.57)	<0.0001
Mean FIB-4 score	1.7 ± 1.6	2.6 ± 2.3	<0.0001
Median FIB-4 score (range)	1.23 (0.19–12.04)	1.72 (0.4–14.51)	<0.0001
Mean Forns score	4.6 ± 1.9	5.8 ± 1.9	<0.0001
Median Forns score (range)	4.48 (0.67–11.45)	5.69 (0.68–11.29)	<0.0001

*Fibrosis estimates are calculated according to published cut-offs [11] and using the METAVIR score.

HIV-negative and HIV-positive individuals: APRI (r = 0.354 and r = 0.406, P < 0.0001, respectively), FIB-4 (r = 0.298 and r = 0.416, P < 0.0001, respectively) and Forns (r = 0.366 and r = 0.379, P < 0.0001, respectively).

Predictors of advanced liver fibrosis

Factors associated with severe fibrosis or cirrhosis (FibroScan ≥9.5 kPa) in monoinfected and coinfected patients, and in the whole population, are recorded in Table 3. By multivariate analysis, only a BMI >25 kg/m^2 (P = 0.001) was significantly associated with advanced liver fibrosis in HCV-monoinfected individuals. In HIV/HCV-coinfected patients, only duration of infection >25 years was significantly associated with advanced liver fibrosis in the multivariate analysis. When all patients were considered, age >45 years (P = 0.03), BMI >25 kg/m^2 (P < 0.0001) and HIV infection were all significantly associated with advanced liver fibrosis. Gender, mode of contamination, duration of infection, HCV genotype, and HCV viraemia were not associated with advanced liver fibrosis.

DISCUSSION

This large study confirms that liver fibrosis is more severe in HIV/HCV-coinfected (39%) patients than in HCV-monoinfected individuals (18%), even when assessing HIV-positive patients with controlled HIV infection under HAART and the exclusion criteria being only individuals planned to be treated with interferon. These findings support the results from prior studies carried out before the introduction of HAART and/or using information derived from liver biopsies [1,7,19]. Although immune recovery under HAART has been associated with a slower progression of HCV-related hepatic damage in HIV-coinfected patients [1,20–22], when comparing patients with and without HIV infection, our results suggest that this benefit on progression in liver fibrosis may not revert completely the deleterious impact of HIV infection. Either some immune dysfunction may still be relevant in this regard or, alternatively, long-term exposure to antiretroviral therapy might impact negatively on liver fibrosis. In confirmation of the latter, insulin resistance caused by some antiretroviral regimens might be associated with hepatic steatosis, which in turn may enhance liver fibrosis [23,24]. Other mechanisms of liver toxicity may work as well accelerating the progression of liver fibrosis in subjects under some antiretroviral agents [25,26].

In the univariate model, a better immune status was associated with milder stages of liver fibrosis in the coinfected population. However, in the multivariate model, immune status lost impact on liver fibrosis when corrected for duration of HIV infection, which indirectly might reflect time under antiretroviral therapy. Besides HIV infection, older age and higher BMI were significantly associated with severe liver fibrosis in our study. This observation is of interest as some of the reports, which have not found differences in hepatic fibrosis differentiating between HCV-monoinfected and HCV/HIV-coinfected patients, have included older persons and/or individuals with high BMI [19], and both factors may have masked the impact of HIV itself.

Our study shows that longer time of HCV infection was associated with more advanced liver fibrosis in HCV/HIV-coinfected individuals, while in HCV-monoinfected patients, a higher BMI was the main determinant of severe liver fibrosis. This finding underscores that duration of HCV infection is a strong negative factor for coinfected patients, most likely on account of its accelerated course. Therefore, HCV/HIV-coinfected patients should be considered for peginterferon–ribavirin therapy as soon as possible. The achievement of HCV clearance may halt liver damage and clinical consequences of liver decompensation [27] and possibly permits at least a partial regression of liver fibrosis [28,29].

Several non-invasive approaches have been developed in recent years to measure hepatic fibrosis, avoiding the need for a liver biopsy. Indexes built using serum fibrosis

Table 3 Factors associated with severe fibrosis or cirrhosis in patients with chronic hepatitis C

	HCV-monoinfected (n = 656)			HCV/HIV-coinfected (n = 287)			All patients (n = 943)		
	Odds ratio	95% confidence interval	P	Odds ratio	95% confidence interval	P	Odds ratio	95% confidence interval	P
Univariate analysis									
Age >45 years	4.53	2.57–8.01	<0.0001	1.20	0.70–2.06	NS	1.38	1.02–1.87	0.04
Male gender	1.13	0.75–1.71	NS	1.73	1.00–2.92	0.04	1.72	1.27–2.32	<0.0001
BMI > 25 kg/m^2	2.57	1.70–3.87	<0.0001	1.10	0.32–3.72	NS	1.97	1.37–2.85	<0.0001
Mode of contamination (transfusion *vs* others)	1.58	1.05–2.38	0.03	0.89	0.25–3.10	NS	0.90	0.64–1.29	NS
Age at HCV infection >25 years	2.67	1.60–4.47	<0.0001	0.38	0.14–1.14	NS	0.99	0.69–1.45	NS
Duration of HCV infection >25 years	1.71	1.05–2.78	0.03	2.56	1.21–5.43	0.01	1.69	1.15–2.48	0.008
HCV genotype non-2, -3	0.92	0.59–1.42	NS	1.17	0.63–2.18	NS	1.05	0.74–1.48	NS
HCV genotype 3	1.11	0.56–2.22	NS	0.83	0.44–1.59	NS	1.15	0.73–1.82	NS
HCV viral load >800 000 IU/L	1.34	0.75–2.42	NS	0.96	0.49–1.90	NS	1.50	0.99–2.28	NS
HIV coinfection	–	–	–	–	–	–	3.01	2.21–4.11	<0.0001
Plasma HIV–RNA > 50 copies/mL	–	–	–	0.66	0.40–1.09	NS	–	–	–
CD4 count <500 cells/μL	–	–	–	1.79	1.04–3.06	0.03	–	–	–
Multivariate analysis									
Age >45 years	2.03	0.90–4.55	NS	–	–	–	2.71	1.51–4.87	0.001
Male gender	–	–	–	1.91	0.87–4.22	NS	1.26	0.75–2.10	NS
BMI > 25 kg/m^2	2.43	1.47–4.03	0.001	–	–	–	2.35	1.44–3.84	0.001
Mode of contamination (transfusion *vs* others)	1.22	0.73–2.03	NS	–	–	–	–	–	–
Age at HCV infection >25 years	1.90	0.97–3.71	NS	–	–	–	–	–	–
Duration of HCV infection >25 years	1.67	0.96–2.91	NS	2.42	1.11–5.28	0.03	1.15	0.89–2.42	NS
HIV coinfection	–	–	–	–	–	–	3.21	1.48–6.97	0.003
CD4 count <500 cells/μL	–	–	–	1.76	0.86–3.62	NS	–	–	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase, NS, not significant.

markers (e.g. APRI, FIB-4 and Forns indexes) and imaging techniques, as FibroScan, have all been proven to correlate quite well with liver fibrosis staging,. evaluated using histology, both in HCV-monoinfected and HIV/HCV-coinfected patients [12–14,16–18,30,31]. In our study, the prevalence of severe fibrosis and cirrhosis was higher in coinfected than in HCV-monoinfected patients using both FibroScan and FIB-4 index. As the cut-off value for the diagnosis of severe fibrosis and cirrhosis using APRI and Forns indexes is not defined, we could not evaluate their predictive value in our series.

Serum biomarkers and FibroScan were highly concordant in our study both in HIV-negative and HIV-positive patients with chronic hepatitis C. The performance of FibroScan for the diagnosis of liver cirrhosis is high and very reproducible [12,14,30,31]. Therefore, this method may become the gold standard for the diagnosis of cirrhosis. Given that FibroScan and simple biochemical tests are strongly concordant, in places where FibroScan is not yet available, the diagnosis of cirrhosis could be made using biochemical tests. The simplicity of these techniques allows to make quick clinical decisions, longitudinal periodic monitoring and check large populations, which is often a limitation for liver biopsy [32]. Clinicians taking care of HCV/HIV-coinfected patients should be more familiar and integrate in their clinical decisions the information derived from these new diagnostic tools.

In summary, HIV/HCV-coinfected patients continue to demonstrate more advanced liver fibrosis than patients with HCV monoinfection in the HAART era. The benefits of antiretroviral therapy slowing down the progression of liver fibrosis as a result of immune recovery may not completely reverse the deleterious impact of HIV immune dysfunction or, alternatively, liver toxicity associated with at least some antiretroviral agents might counterbalance it. While waiting for more effective anti-HCV drugs to come, provision of currently available HCV treatment should be considered as a priority for HIV/HCV-coinfected patients.

CONFLICT OF INTEREST

Authors have no conflict of interest and have contributed to, seen and approved the manuscript.

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