Regression of liver fibrosis is progressive after sustained virological response to HCV therapy in patients with hepatitis C and HIV coinfection

J. L. Casado, C. Quereda, A. Moreno, M. J. Pérez-Elías, P. Martí-Belda and S. Moreno *Department of Infectious Diseases, Ramón y Cajal Hospital, Madrid, Spain*

SUMMARY. There are few data about the long-term histological outcome of HIV-/HCV-coinfected patients after therapy with interferon and ribavirin. We performed an observational study of 216 patients who received therapy against HCV and who had at least three successive transient elastographies (TE) during the follow-up. The primary endpoint was confirmed fibrosis regression, defined as a reduction of at least 1 point in Metavir fibrosis score, confirmed and without worsening in successive TE. At baseline, 23% had fibrosis stage 4 or cirrhosis. Overall, 82 (38%) achieved sustained virological response (SVR), without differences in baseline fibrosis or time of follow-up. Confirmed fibrosis regression was observed in 55% of patients, higher for SVR (71% *vs* 44%; *P* < 0.01), and the likelihood of achieving fibrosis regression at 3, 5 and 7 years was 0.17, 0.51 and 0.67, respectively, for SVR patients, in comparison with 0.02, 0.23 and 0.41 for no SVR patients (*P* < 0.01, log-rank test at any time point). Progressive regression, defined as continuous improvement in successive TE, was observed in 62% of patients with advanced liver fibrosis or cirrhosis who achieved SVR. In a Cox regression model, only SVR (HR, 4.01; 95% CI, 2.33–7.57; *P* < 0.01) and a younger age (HR, 1.14; 95% CI, 1.05–1.25; *P* < 0.01; per year) were associated with fibrosis regression. This study confirms that the rate of liver fibrosis regression increases during the follow-up after SVR to interferon therapy in HIV-/HCV-coinfected patients.

Keywords: fibrosis, hepatitis C, histological, interferon therapy, regression, transient elastography.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is cause of more rapid progression of fibrosis and development of cirrhosis in patients coinfected with hepatitis C virus (HCV) [1,2]. For this reason, HIV-infected individuals with positive HCV RNA determinations should be considered as potential candidates for anti-HCV treatment [3,4].

Together with the disappearance of HCV replication, it is already known that response to antiviral therapy with interferon or ribavirin reduces liver complications in chronic hepatitis C [5,6], and there is sufficient evidence of histological improvement in HCV-monoinfected patients after sustained virological response (SVR) [7,8]. However, little is known about the long-term evolution of liver fibrosis in HIV-/HCV-coinfected patients following therapy against HCV, taking into account the differences in fibrogenesis or viral kinetics, and the influence of immunosuppression [9]. There could be expected slight changes in fibrosis, a similar outcome to that of monoinfected, or even better if the role of inflammation is higher [10].

In addition, during the last years, a noninvasive technique, transient elastography (TE), has been shown to identify fibrosis stage accurately [11]. Liver stiffness measurement through TE is reproducible and independent of the operator [12] and explores a volume of liver parenchyma, which can be approximated to a cylinder of 1 cm in diameter and 4 cm in length. This volume is 100 times larger than the biopsy specimen volume and is thus much more representative of the entire hepatic parenchyma. Therefore, this technique could permit to repeat fibrosis evaluation in treated and untreated patients, evaluating changes along the time in liver fibrosis, without the biopsy-associated risk of morbidity [13].

Thus, the aim of this study was to determine the effect of achieving an SVR on long-term histological outcomes,

specifically in terms of progressive fibrosis improvement, and the usefulness of TE in the follow-up of HIV-/HCV-co-infected patients.

PATIENTS AND METHODS

Design and patient selection

This observational cohort study was composed of patients treated with pegylated interferon and ribavirin and was established in 2007 to follow up by TE patients coinfected with HIV/HCV who started therapy with these drugs at our unit since 2004. As inclusion criteria, patients should have a baseline fibrosis determination by liver biopsy or by TE, should have received anti-HCV therapy with pegylated interferon plus ribavirin, and should also have at least three consecutive determinations of fibrosis by TE during the follow-up.

The decision to administer anti-HCV therapy to coinfected patients was taken by the responsible physician according to national and international guidelines established in that time. Patients were counselled against the use of alcohol.

The primary objective of this cohort study was to determine the effect of achieving an SVR after therapy with interferon and ribavirin on the long-term fibrosis outcome of coinfected patients. The study cohort received the approval of the ethics committee of our centre (EC 150/06).

Procedures

For each patient, we extracted the following data at the initiation of therapy with interferon plus ribavirin: age, sex, risk factor for HIV acquisition, prior acquired immunodeficiency syndrome (AIDS)-defining condition, baseline and nadir CD4+ cell counts, and baseline HIV viral load. We also recorded information about HAART, including type, and date of initiation. Information related to HCV infection included genotype, HCV RNA levels and estimated year of HCV infection, which was estimated for injection drug users by assuming that it started the first year needles were unsafely shared. Duration of HCV infection was considered since the first positive analysis for patients infected through sexual contact.

Before therapy against HCV was initiated, a liver biopsy or a TE was performed. An experienced pathologist analysed liver biopsy samples obtaining the histological activity index (HAI), and a staging of fibrosis according to the modified Knodell scoring system as follows: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis or rare portal–portal septa; F3, fibrous septa with architectural distortion and no obvious cirrhosis (bridging fibrosis); and F4, definite cirrhosis [14].

Transient elastography (FibroScan, Echosens, Paris, France), was performed since 2007 by trained operators, according to manufacturer's recommendations [15].

Briefly, to be considered acceptable, each evaluation was performed fasting, included at least 10 measurements and have to reach an 80% of successful measurements and <30% of interquartile variations. In cases of discordance between measurements, the number could be elevated to 20, but the rate of success and interquartile range were not permitted to change. Liver fibrosis was established according to stiffness cut-off criteria defined by Castera *et al.* [16]: 7.2 kiloPascals (kPa), 9.5 and 12.5 kPa for fibrosis stage 2, 3 and 4, respectively. As example, this cut-off of 12.5 kPa had a positive and negative predictive value of 77% and 95%, respectively, for the diagnosis of fibrosis 4 or cirrhosis.

Outcome and endpoints

Sustained virological response was defined as an undetectable serum HCV RNA level 24 weeks after discontinuation of therapy. Patients not fulfilling SVR criteria, including those who relapsed after achieving end of treatment response, were classified as non-SVR.

The primary endpoint, confirmed fibrosis regression, was defined as a confirmed reduction of at least one point in fibrosis Metavir score during the follow-up (i.e. from fibrosis 3 to fibrosis 2) without worsening in successive TEs. As this outcome was not applicable to patients with fibrosis 1, persistence in this level was separately evaluated, together with changes in stiffness measurements during the follow-up, as measured in kilopascals. In the overall population, we also calculated the progression index of liver fibrosis before and after treatment. The progression index was obtained by dividing the degree of fibrosis (by Metavir score) observed in the pretreatment liver biopsy or TE by the duration of HCV infection in years, and it was repeated obtaining the ratio between the degree of fibrosis in the post-treatment measurement (the 3rd TE), divided by the total number of years. Finally, to identify individual patients with progressive benefit, we analyse those patients who had a continuous decrease of at least 1 point in two successive TE (i.e. from fibrosis 3 to 2, and fibrosis from 2 to 1), without progression. This endpoint was only applicable to patients with fibrosis 3–4 at baseline.

For patients who had more than one period of therapy, failing the first episode, only the last was included in the analyses of the association between response and fibrosis improvement. The length of the study was calculated from the date of SVR (6 months after end of therapy) and ended at the date of the last clinical visit available prior to July 2012.

Statistics

We calculated the frequencies (mean or median, interquartile ranges, IQR) and estimates of the survival function (Kaplan–Meier) of the primary endpoint, confirmed fibrosis

regression. Baseline characteristics and differences between groups were analysed using the chi-square test, Student's *t*-test or Mann–Whitney *U* test, as appropriate. For repeated stiffness determinations (kilopascals), the Wilcoxon rank-sum test for repeated measurements was used. A Cox regression model was used to explore baseline factors predicting fibrosis regression.

RESULTS

Between January 2004 and December 2011, 404 patients received anti-HCV therapy, and 216 patients had three TE during the follow-up and therefore met the inclusion criteria. Their baseline characteristics are shown in Table 1. In brief, 79% were male, mean age was 41.1 years, 29% had a prior AIDS-defining condition, the median baseline CD4+ cell count was 529 cells/mm³, 71% had an HIV RNA level below 50 copies/mL, the median time since HCV infection was 21 years (IQR, 18–24), and 51% were infected by HCV genotype 1. Liver biopsy was performed in 149 cases (69%) and TE in 67 patients before anti-HCV therapy was started, and it revealed that 49 patients (23%) had fibrosis 4 or cirrhosis. A TE was performed in 25 patients at the same time of liver biopsy, showing a high concordance ($r = 0.8$), as previously known. Strikingly, the median time from biopsy or baseline TE to VHC therapy was 9.16 months (1.8–29.8). Before therapy, estimated fibrosis progression rate (FPR) was 0.11 per year (0.06–0.15). There were no cases of significant alcohol consumption (>30 g/day) during the follow-up.

All the patients received pegylated interferon plus ribavirin for a median time of 329 days (200–358). During treatment of hepatitis C, 181 (84%) patients were on HAART. The most common combinations were two nucleoside reverse transcriptase inhibitor (NRTI) drugs plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) drug in 119 patients (55%) and two NRTI plus one protease inhibitor in 76 patients (35%). Overall, 82 (38%) of

Table 1 Baseline characteristics of the 216 patients included

Variable	Overall (n = 216)	SVR (n = 82, 38%)	Non-SVR (n = 134, 62%)	P value
Mean age (years, IQR)	41.1 (38–44)	41.4 (38–45)	41 (38–44)	0.5
Sex: male (%)	171 (79)	65 (79)	106 (79)	0.9
IDU as risk factor (%)	192 (89)	74 (90)	118 (89)	0.91
Previous AIDS (%)	63 (29)	25 (30)	38 (28)	0.67
On HAART (%)	181 (84)	67 (82)	112 (84)	0.4
Nadir CD4+ count (cells/mm³)	190 (83–296)	195 (73–310)	180 (87–295)	0.27
Baseline CD4+ (cells/mm³)	529 (380–717)	546 (442–730)	517 (355–701)	0.2
Baseline HIV RNA level (log copies/mL)	1.7 (1.7–1.9)	1.7 (1.7–1.8)	1.7 (1.7–2.2)	0.28
	71% < 50 c/mL	74%	69%	
Mean time of HCV infection (years)	21 (18–24)	20.1 (17–24)	21.1 (18–24)	0.4
HCV viral genotype (%)				
1	111 (51)	29 (35)	82 (61)	<0.01
2	2 (1)	2 (2)	–	
3	67 (31)	39 (48)	28 (21)	
4	36 (17)	12 (15)	24 (18)	
RNA HCV (log, UI/mL)	5.9 (5.4–6.3)	5.6 (5–6.1)	6.2 (5.6–6.4)	<0.01
Fibrosis at baseline (%)				
1	69 (32)	26 (32)	43 (32)	0.7
2	57 (26)	19 (23)	38 (28)	
3	41 (19)	18 (22)	23 (17)	
4	49 (23)	19 (23)	30 (22)	
HAI*	5.74 (4–7)	6.9 (5–8)	5.27 (4–7)	0.039
APRI	1.5 (0.6–1.82)	1.37 (0.66–1.66)	1.88 (0.61–2.1)	0.04
FPR (Metavir units/year)	0.11 (0.06–0.15)	0.13 (0.11–0.15)	0.11 (0.06–0.15)	0.8
Time from baseline biopsy/TE to therapy (months)	9.16 (1.8–29.8)	14.4 (3.2–38)	6.1 (1.4–27.8)	0.01
Time of anti-HCV therapy (days)	329 (200–358)	343 (329–377)	263 (186–336)	<0.01
Time of follow-up after therapy (months)	89 (66.7–116)	78.4 (57.6–99.2)	93.3 (73.4–117)	0.02
Deaths (n)	4	2	2	0.9

SVR, sustained virological response; HAI, histological activity index (*available only in 149 cases with liver biopsy); APRI, AST-to-platelet ratio; FPR, fibrosis progression rate.
Values are expressed as median and interquartile range (IQR), unless otherwise specified.
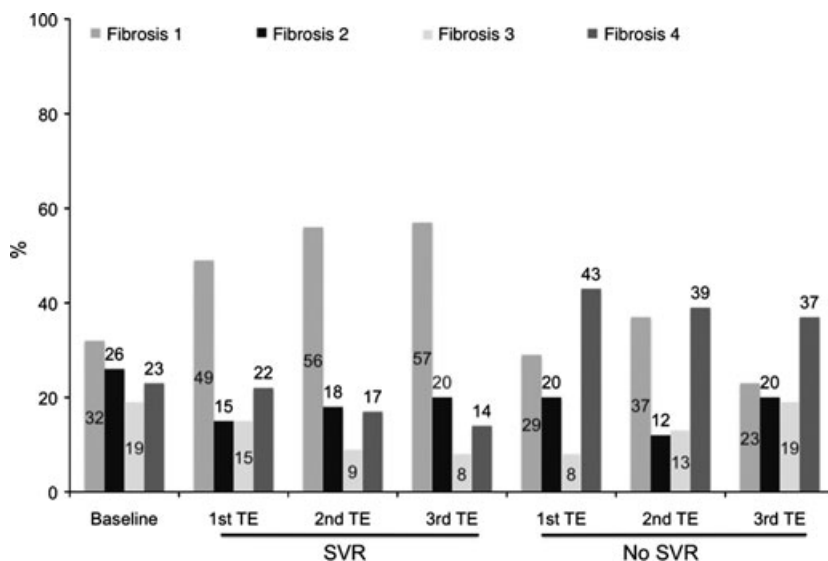
Fig. 1 Percentage of fibrosis degree during the successive transient elastographies (TE), overall and according to sustained virological response (SVR).

the patients achieved a SVR. Differences in baseline and clinical characteristics between responders are shown in Table 1, remarking the role of viral genotype and HCV RNA in achieving SVR. Of note, baseline fibrosis or FPR before therapy was not different according to response, and time of follow-up was higher in patients without SVR.

Fibrosis regression

Three consecutive TE were performed in a median time of 34 (10.6–61), 51 (30–83.1) and 60 (43.2–86.1) months after SVR evaluation, respectively. The median time from biopsy or baseline TE to the first TE was 46.1 months. Despite that, as shown in Fig. 1, the number of patients having fibrosis 1 increased along the TE measurements, whereas the rate of patients with fibrosis 4 decreased, especially in the first and second TE. This fact was a consequence of the high percentage of patients having fibrosis improvement (for those with fibrosis 2 to 4 at baseline) or persistence (patients with baseline fibrosis 1), as shown in the Fig. 2. Thus, for the 147 patients (68%) having fibrosis 2 to 4 at baseline, fibrosis regression was observed in 39%, 41% and 42% at the three successive TEs, respectively. On the other hand, worsening or fibrosis progression was observed in 27%, 26% and 21%. For the 69 patients (32%) having fibrosis 1 at baseline, persistence at this degree was observed in 59%, 59% and 46% of cases. Also, there was a marked decrease in the median stiffness values during the three consecutive TE (from 8.8 to 8.35 to 8.2, $P = 0.08$ for TE1 *vs* TE2; Wilcoxon rank-sum test; Table 2). Confirmed fibrosis regression, as strictly defined, was
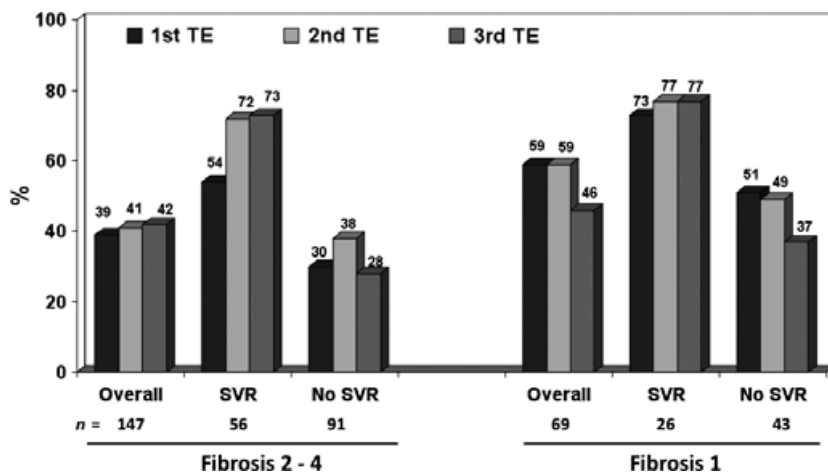

Fig. 2 Fibrosis regression (for patients with baseline F2 to F4) and persistence (for patients with baseline F1) in three successive transient elastographies (TE), overall and according to sustained virological response (SVR).

Table 2 Evolution of median stiffness values (kPa) and fibrosis progression rate during the three successive transient elastographies

	Baseline	1st TE		2nd TE		3rd TE		P value
		SVR	No SVR	SVR	No SVR	SVR	No SVR	
Time after therapy, months	-	26.8 (9.2–53.7)	37.1 (18.7–62.7)	51 (36.1–77.6)	52.1 (41.6–83.5)	52.9 (34.8–64.1)	64.3 (44.7–85.9)	NA
Stiffness values (kPa)	9.2*	7.4 (5.4–11.8)	9.35 (6.7–17.6)	6.7 (4.3–9.6)	10.15 (6–17.4)	6.3 (4.6–9.1)	10.1 (7.3–19.3)	<0.01
FPR (Metavir units/year)	0.11	–	–	–	–	0.052	0.108	<0.01

TE, transient elastography; SVR, sustained virological response; kPa, kilopascals; FPR, fibrosis progression rate.

Values are expressed as median and interquartile range, unless otherwise specified.

*Available only for 92 patients.

observed in 81 of the 147 patients (55%), and also progressive fibrosis regression for patients with fibrosis 3 or 4 was observed in 32 of 90 patients (36%). After therapy, FPR was 0.0012 Metavir units/year, and globally, at the third TE, FPR was reduced to 0.08 (0.047–0.13) per year. In a Kaplan–Meier analysis, the likelihood of fibrosis regression at 3 and 5 years was 0.09 and 0.35, respectively.

Fibrosis outcome according to SVR

As shown in Table 2 and Fig. 1, the histological benefit was observed especially in those patients with SVR. In a similar time of follow-up, fibrosis regression was observed in 54%, 72% and 73% of patients with SVR, respectively, higher than that observed in patients without SVR ($P < 0.01$ in all comparisons). Of note, of the 91 patients without SVR having fibrosis 2 to 4 at baseline, 27 (30%) and 34 (38%) improved at the first and second TE, and 26 persisted as fibrosis improvement at the third TE (28%). Confirmed fibrosis regression was achieved in 71% in SVR *vs* 44% in non-SVR patients ($P < 0.01$). In a Kaplan–Meier analysis, the likelihood of fibrosis regression at 3, 5 and 7 years was 0.17, 0.51 and 0.67 for SVR, in comparison with 0.02, 0.23 and 0.41 for non-SVR patients ($P < 0.01$, log-rank test; Fig. 3). Also, persistence in fibrosis 1 was observed in almost all patients with SVR (77% *vs* 37%, $P < 0.01$). Strikingly, progressive fibrosis improvement in successive TEs was observed in 62% *vs* 21% of patients with fibrosis 3–4 ($P < 0.01$; log-rank test). Furthermore, after SVR, median stiffness value decreased significantly (from 7.4 to 6.7 to 6.3 kPa, respectively; $P < 0.01$), with differences to no SVR patients. Also, FPR post-therapy was lower in SVR whereas it remained similar to baseline if not SVR (0.052 *vs* 0.10 Metavir units/year, $P < 0.01$), as shown in Table 2. From a clinical point of view, for an
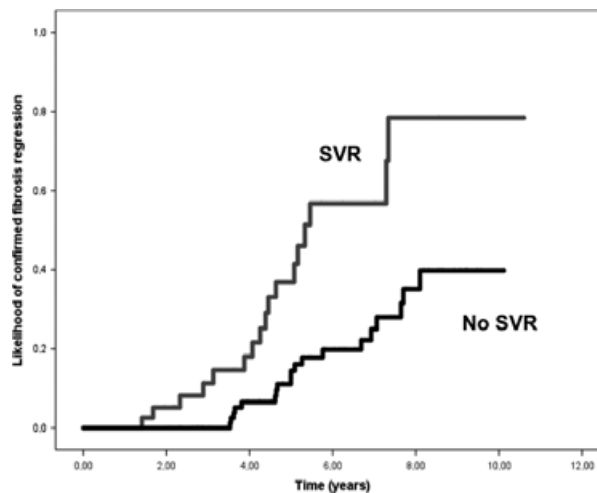

Fig. 3 Likelihood of fibrosis regression according to sustained virological response (SVR).

Table 3 Univariate and multivariate hazard ratios (HRs) of confirmed fibrosis regression among 216 patients with hepatitis C and human immunodeficiency virus (HIV) coinfection

Variable	Univariate analysis (hazard ratio, HR, 95% CI)	P value	Multivariate analysis (hazard ratio, HR, 95% CI)	P value
Younger age (per year)	1.09 (1.04–1.14)	<0.01	1.14 (1.05–1.25)	<0.01
Viral genotype (2–3 *vs* 1–4)	2 (1.02–3.84)	0.04	1.12 (0.86–3.34)	0.26
Duration of HCV therapy (per day)	1.003 (1.001–1.006)	0.04	1.01 (0.99–1.012)	0.8
SVR	3.57 (1.81–7.14)	<0.01	4.01 (2.33–7.57)	<0.01

HCV, hepatitis C virus; SVR, sustained virological response.

accumulated time of follow-up of 1594.1 patient-years (median time 89 months), only four patients died (2.4%), in three cases related to liver complications.

Factors associated with fibrosis regression

By univariate analysis, fibrosis regression was associated with longer time on therapy (316 *vs* 250 days, $P = 0.04$), viral genotype 2–3 *vs* 1–4 ($P = 0.04$), a younger age ($P < 0.01$) and to SVR ($P < 0.01$), and not to sex, CDC stage, use of HAART, nadir or baseline CD4+ count, HCV RNA or fibrosis stage. As expected, as a longer time on therapy and viral genotype were closely related to SVR, in a Cox regression analysis we found that only SVR and age were statistically associated with fibrosis regression (Table 3). The adjusted hazard ratio of fibrosis regression was 4.01 (95% CI, 2.33–7.57; $P < 0.01$) for SVR and 1.14 (95% CI, 1.05–1.25; $P < 0.01$ per year) for age.

DISCUSSION

In the present study, we evaluated the histological liver improvement in a large cohort of HIV-/HCV-coinfected patients who were followed up through TEs for a median of approximately 60 months after therapy with interferon plus ribavirin. We found that, with a confirmatory definition of fibrosis regression, 71% of patients with fibrosis 2 or higher who achieved SVR had fibrosis improvement, markedly better than those who did not. Furthermore, our data underscore that this improvement is progressive along the time, confirming the middle- and long-term benefit of achieving SVR in HIV-/HCV-coinfected patients.

Cumulative evidence in HCV-monoinfected patients suggests that SVR may halt and even reverse hepatic fibrosis [7,8,17]. However, to date, little was known about the long-term consequences of achieving SVR in patients coinfected with HIV/HCV. In a subanalysis from the multinational APRICOT Trial, paired liver biopsies obtained from 401 patients showed that histological response rate ranged from 62% to 74% in patients who achieved a SVR, although the follow-up was limited to 24 weeks and the definition was a reduction of 1 point in the Ishak fibrosis

score [18]. Likewise, in a subanalysis from the ANRS HC02 RIBAVIC trial with paired liver biopsies from 198 patients, the authors found that failure to achieve SVR was significantly associated with worsening of liver fibrosis [9]. In a small study including 67 monoinfected and 41 coinfected patients, fibrosis scores improved by 1 point in 42.5% of coinfected cases, without differences between HIV-positive and HIV-negative patients, but again histological assessment was performed 2 years after the end of interferon therapy [19]. A similar outcome was observed in 47.0% of the coinfected patients who attained SVR [20].

Our study suggests that the extent of follow-up is important. The majority of post-treatment biopsies are taken around 6 months after, and fibrosis improvement is a slow process. Thus, fibrosis and inflammation can regress after successful treatment for HCV, but it is still unknown as to what extent and to how long it is happening [21,22]. It could be hypothesized that a decrease in liver stiffness during the first months after treatment could be related to a reduction in liver inflammation. Our study, with the longest follow-up of treated patients, confirms that this hypothetical reduction in inflammation is followed by a longer period of regression of fibrosis, if SVR to therapy has been achieved, as previous studies suggest [23,24]. Moreover, it confirms that HIV coinfection does not compromise liver histological response to interferon therapy [19].

The ultimate cause of this progressive improvement is not fully elucidated. The marked rate of fibrosis regression could be explained by the pathogenesis of HCV in HIV infection. Coinfection increases apoptosis of hepatocytes and activation of hepatic stellate cells (HSC) [25,26]. HIV infection and activation of HSC are the proven precursors of liver fibrosis, promoting collagen expression and secretion of proinflammatory cytokines [26,27]. On the other hand, reversion of fibrosis is accompanied by clearance of HSC by apoptosis, and studies in rodents have demonstrated that experimental augmentation of HSC apoptosis will promote the resolution of fibrosis [28,29]. Taken together, the extent of HSC clearance achieved during interferon therapy could explain the long-term benefit, in the basis of controlled HIV infection [30]. In this way, the

influence of age in fibrosis regression observed in several studies [31], including this, supports the influence of HSC, as older age is associated with hyperplasia of HSC in animal models [32].

Although significantly lower, histological responses were obtained in an important proportion of patients who did not achieve SVR during treatment, as previously described [18,20]. This fact has been attributed to inflammation reduction, and it could be expected to be transient, with later worsening [33]. However, our study demonstrates that 44% continued to have fibrosis regression even 5 years after therapy. Thus, the above-described mechanisms could be important for a small proportion of patients who could have a marked benefit with interferon therapy, even without SVR. However, larger studies have failed to demonstrate the clinical benefit of continuing low doses of interferon in patients with advanced disease without SVR [34], and other factors such as the continuous control of HIV replication could be involved. Thus, further efforts should be made to identify the factors associated with histological improvement, independently of response.

In any case, this improvement in fibrosis could fully explain the clinical benefit observed in HIV-/HCV-coinfected patients after SVR. Several studies have shown that SVR was associated with a significant reduction in the hazard of clinical events [6,35]. Nevertheless, in a cohort of 455 patients followed prospectively for a median of 9 years, response to interferon was a predictor of complications by univariate analysis, but failed to reach significance after adjustment for the fibrosis score in the multivariate model, suggesting that liver fibrosis is the final determinant of associated complications [5]. Available evidence also suggests that even patients with compensated liver cirrhosis who achieve SVR may experience beneficial alterations of their disease course [36]. The results of our study suggest that treatment and clearance of HCV can halt and even progressively reverse cirrhosis, with most of cirrhotic patients having sustained improvement after 5 years. Only four patients in our cohort died during the follow-up (2%), when 23% were initially cirrhotic. However, we have not studied the incidence of associated complications, such as hospital admission or hepatocellular carcinoma. This highlights the importance of continued surveillance of these patients.

Our study has several limitations, the most important being that it is not entirely prospective. However, patients were followed closely by the same physicians in the same hospital throughout the course of their disease. Furthermore, the continued follow-up of patients could bias the study to include patients with a better outcome and therefore with greater liver fibrosis benefit. However, baseline fibrosis was similar, and time of follow-up was even longer in patients without SVR. Finally, liver fibrosis was determined through TE, and the accuracy of TE in assessing fibrosis may be questioned because of sampling error and relatively low discriminating power [37]. In the present study, cut-off values for fibrosis 2 (7.2 kPa) and fibrosis 4 (12.5 kPa) were slightly different from those published in a meta-analysis [38], which could modify the number of patients classified in each fibrosis degree. In any case, the same cut-off values were used along the study, and specially, the strict definition of fibrosis regression, requiring three confirmatory measurements without worsening, supports our findings.

In summary, our study shows that SVR to hepatitis C therapy is associated with confirmed and progressive fibrosis regression in patients coinfected with HIV/HCV, even 5 years after therapy. Around a third of patients without SVR showed liver fibrosis improvement. This histological improvement could explain the clinical benefit associated with SVR, as previously described. These findings emphasize the need to prioritize adequate management of chronic HCV infection, one of the most clinically relevant comorbid conditions in the HIV-infected population.

ACKNOWLEDGEMENTS AND DISCLOSURE

REFERENCES

1 Graham CS, Baden LR, Yu E *et al.* Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; 33: 562–569.

2 Soto B, Sanchez-Quijano A, Rodrigo L *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997; 26: 1–5.

3 Torriani FJ, Rodriguez-Torres M, Rockstroh JK *et al.* Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351: 438–450.

4 Chung RT, Andersen J, Volberding P *et al.* Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; 351: 451–459.

5 Coverdale SA, Khan MH, Byth K *et al.* Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. *Am J Gastroenterol* 2004; 99: 636–644.

6 Veldt BJ, Heathcote EJ, Wedemeyer H *et al.* Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007; 147: 677–684.

7 Camma C, Di Bonna D, Schepis F et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. *Hepatology* 2004; 39: 333–342.

8 Poynard T, McHutchison J, Manns M et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; 122: 1303–1313.

9 Bani-Sadr F, Lapidus N, Bedossa P et al. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. *Clin Infect Dis* 2008; 46: 768–774.

10 Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008; 22: 1979–1991.

11 Operskalski EA, Kovacs A. HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Curr HIV/AIDS Rep* 2011; 8: 12–22.

12 Neukam K, Recio E, Camacho A et al. Interobserver concordance in the assessment of liver fibrosis in HIV/HCV-coinfected patients using transient elastometry. *Eur J Gastroenterol Hepatol* 2010; 22: 801–807.

13 Ogawa E, Furusyo N, Toyoda K, Takeoka H, Maeda S, Hayashi J. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. *Antiviral Res* 2009; 83: 127–134.

14 The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; 20: 15–20.

15 Moreno S, Garcia-Samaniego J, Moreno A et al. Non invasive diagnosis of liver fibrosis in patients with HIV infection and HBV/HCV coinfection. *J Viral Hepat* 2009; 16: 249–258.

16 Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008; 48: 835–847.

17 George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology* 2009; 49: 729–738.

18 Lissen E, Clumeck N, Sola R et al. Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. *AIDS* 2006; 20: 2175–2181.

19 Di Martino V, Thevenot T, Boyer N et al. HIV coinfection does not compromise liver histological response to interferon therapy in patients with chronic hepatitis C. *AIDS* 2002; 16: 441–445.

20 Sarmiento-Castro R, Horta A, Vasconcelos O et al. Impact of peginterferon alpha-2b and ribavirin treatment on liver tissue in patients with HCV or HCV e HIV co-infection. *J Infect* 2007; 54: 609–616.

21 Sobesky R, Mathurin P, Charlotte F et al. Modelling the impact of interferon treatment on liver fibrosis progression in chronic hepatitis c: a dynamic view. The Multivirc Group. *Gastroenterology* 1999; 116: 378–386.

22 Marcellin P, Boyer N, Gervais A et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alfa therapy. *Ann Intern Med* 1997; 127: 875–881.

23 Andersen ES, Moessner EK, Christensen PB et al. Lower liver stiffness in patients with sustained virological response 4 years after treatment for chronic hepatitis C. *Eur J Gastroenterol Hepatol* 2011; 23: 41–44.

24 Barreiro P, Labarga P, Martin-Carbonero L et al. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. *Antivir Ther* 2006; 11: 869–877.

25 Jang JY, Shao RX, Lin W et al. HIV infection increases HCV-induced hepatocyte apoptosis. *J Hepatol* 2011; 54: 612–620.

26 Bruno R, Gallastri S, Sacchi P et al. gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. *Gut* 2010; 59: 513–520.

27 Chakraborty JB, Oakley F, Walsh MJ. Mechanisms and biomarkers of apoptosis in liver disease and fibrosis. *Int J Hepat* 2012; 2012: Article ID 648915. doi: 10.1155/2012/648915.

28 Friedman SL. Fibrogenic cell reversion underlies fibrosis regression in liver. *Proc Natl Acad Sci USA* 2012; 109: 9230–9231.

29 Kisseleva T, Brenner DA. Hepatic stellate cells and the reversal of fibrosis. *J Gastroenterol Hepatol* 2006; 21(Suppl 3): S84–S87.

30 Giannelli G, Bergamini C, Marinosci F et al. Antifibrogenic effect of IFN-α2b on hepatic stellate cell activation by human hepatocytes. *J Interferon Cytokine Res* 2006; 26: 301–308.

31 Tsubota A, Kumada H, Chayama K et al. Time course of histological changes in patients with a sustained biochemical and virological response to interferon-alpha therapy for chronic hepatitis C virus infection. *J Hepatol* 1997; 27: 49–55.

32 Warren A, Cogger VC, Fraser R, DeLeve L, McCuskey RS, Le Couteur DG. The effects of old age on hepatic stellate cells. *Curr Gerontol Geriatr Res* 2011; 2011: Article ID 439835. doi: 10.1155/2011/439835.

33 Collazos J, Asensi V, de la Fuente B, Cartón JA. The Effect of Unsuccessful Treatment with Peginterferon and Ribavirin on the Liver Fibrosis Course of HIV/HCV-coinfected Patients. *Curr HIV Res* 2012; 10: 679–687.

34 Shiffman ML, Morishima C, Dienstag JL et al. Effect of HCV RNA suppression during peginterferon alfa-2a maintenance therapy on clinical outcomes in the HALT-C trial. *Gastroenterology* 2009; 137: 1986–1994.

35 Berenguer J, Alvarez-Pellicer J, Miralles P et al. Sustained virological response to interferon plus ribavirin reduces liver related complications and mortality in patients coinfected with human immunodeficiency virus

and hepatitis C virus. *Hepatology* 2009; 50: 407–413.

36 Bruno S, Stroffolini T, Colombo M *et al.* Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; 45: 579–587.

37 Sanchez-Conde M, Montes-Ramirez ML, Miralles P *et al.* Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. *J Viral Hepat* 2010; 17: 280–286.

38 Stebbing J, Farouk L, Panos G *et al.* A meta-analysis of transient elastography for the detection of hepatic fibrosis. *J Clin Gastroenterol* 2010; 44: 214–219.