NEW MICROBIOLOGICA, **30**, 259-264, 2007

Rate of cirrhosis progression reduced in HIV/HCV co-infected non-responders to anti-HCV therapy

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SUMMARY

This is a retrospective longitudinal follow-up study of 25 HIV/HCV positive cirrhotic patients not responding to peg-IFN plus ribavirin, and 25 untreated controls matched for age (±5 years), gender and Child-Pugh score.
The primary endpoint of the study was the incidence of cirrhosis progression (CP) defined as the occurrence of at least one of the following events: death, ascites, jaundice, encephalopathy, gastrointestinal bleeding and hepatocellular carcinoma (HCC).
During the median follow-up of 54 months (34-89), four treated (16%) and 13 untreated patients (52%) experienced CP (p=0.02).
Poisson's regression model showed that the independent predictors of CP were Peg-IFN therapy (p=0.016), positive HIV-RNA (p=0.024), and altered ALP values (p=0.012).
Peg-IFN therapy seems to slow down the rate of cirrhosis progression also in HIV/HCV co-infected patients non-responders to anti-HCV therapy, in comparison with untreated patients.

KEY WORDS: Cirrhosis progression, HIV/HCV co-infection, Non-responders, Peg-IFN

The advent of highly active anti-retroviral therapy (HAART) has reduced the mortality caused by AIDS, but increased the other causes of non-HIV-related death. In this context, end-stage liver disease (ESLD) has emerged as a leading cause of morbidity and mortality in HIV/HCV co-infected patients (Mocroft, *et al.*, 2005)
The rapid progression of liver fibrosis and the relatively poor rates of response to treatment for HCV infection (the overall sustained response rate in co-infected patients range from 27-44%) have led some experts to consider co-infected patients with ESLD as candidates for liver transplantation (Torriani, *et al.*, 2004, Carrat, *et al.*, 2004, Soriano, *et al.*, 2004, Ragni, *et al.*, 2003, Pineda, *et al.*, 2005).
The survival of HIV-infected patients with decompensated cirrhosis is much shorter than in HIV-negative patients, and so those awaiting liver transplantation have a very high rate of mortality (Norris, *et al.*, 2004, Miro, *et al.*, 2006).
These considerations underline the need for alternative treatment strategies for cirrhotic patients refractory to pegylated interferon (peg-IFN), in whom the therapeutic choices vary from re-treatment in cases whose previous regimen was inadequate (low drug dose, side effects) to the use of high-dose peg-IFN for viral eradication or low-dose peg-IFN for disease prevention.
The aim of this study was to compare the clinical effect of anti-HCV therapy in lowering the incidence of liver cirrhosis progression in HIV/HCV co-infected patients failing to show a sustained virological response with that observed in untreated patients.
We retrospectively reviewed 50 HIV/HCV posi-

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tive patients attending our centre between September 1997 and October 2005: 25 who had not received any treatment for HCV, and 25 who had failed to respond to at least three months' treatment with peg-IFN plus ribavirin. The treated patients had failed to respond to peg-IFN and ribavirin at different doses depending on body weight and genotype.

At baseline, these patients showed no other causes of chronic hepatitis, and no signs of hepatocellular carcinoma or clinical complications of cirrhosis (ascites, gastrointestinal bleeding, hepatic encephalopathy or jaundice). None of them were alcohol abusers (alcohol intake ≤60 g/day), and none were HbsAg positive.

A record was made for each patient including age, gender, CDC classification, type of HAART, CD4 T cell count, HIV/HCV viral load and ALT enzyme values during the three months before starting treatment. The results of serum HCV and HBV tests; bilirubin, gamma-glutamil transpeptidase, alkaline phosphatase, cholinesterase and albumin levels and esophageal endoscopy were also included. Liver histology was considered when available, the amount of fibrosis was staged by using the Ishak's modified hepatic activity index. Clinical events were recorded every three months. This study was approved by the institutional ethical committee.

The treated and untreated patients were matched for age (quinquennia), gender, and Child-Pugh scores.

The total duration of follow-up was calculated from the date of study entry until death or the occurrence of clinical events related to cirrhosis progression (CP). Death was classified as liver related (clinical events related to CP) or not.

The primary endpoint of the analysis was the rate of CP, defined as the number of clinical events per 100 person-years of follow-up (PYFU). CP was defined as the occurrence of one or more of the following events: liver-related death (liver failure, gastrointestinal bleeding, renal failure), ascites, jaundice, encephalopathy, gastrointestinal bleeding or HCC. All of the clinical events reported up to 31 December 2005 (the date of data-freezing for analysis) were described by the patients' attending physicians and then reviewed by three of these, who are known experts in HIV/HCV co-infection and who were blinded to patients' history. An event was classified as being related to cirrhosis if at least two of the three reviewers agreed that the main cause of disease progression was cirrhosis.

The other study endpoints were the proportion of patients with at least one clinical event, and the time to the first clinical event.

The continuous variables are expressed as median values (IQR) and their independent distributions were compared using the Mann-Whitney rank-sum test; the categorical variables are expressed as frequencies (%) and the associations between them were tested using the chi-square or Fisher's exact test.

The Kaplan-Meier method was used to estimate the probability of cirrhosis progression, as well as the 25^{th} (Q1) and 50^{th} percentiles (median) of the time to cirrhosis progression. The differences between the treated and untreated patients were assessed using the log-rank test. In this analysis, the follow-up was censored at the time of CP or on 31 December 2005.

The CP rate was calculated as the number of clinical events per 100 person-years of follow-up (PYFU).

Univariate and multivariable Poisson regression models were fitted in order to assess the risk of CP and the corresponding 95% confidence. In these models, the months of follow-up were included in order to adjust for the confounding due to the duration of the follow-up. The multivariable models also included the following potential confounders: baseline HIV-RNA, nadir CD4 count, baseline hemoglobin, baseline alkaline phosphatase, baseline pseudo-cholinesterasis, baseline PLT, baseline total bilirubin, baseline PT, baseline transaminase (ALT), and the use of HCV therapy.

All analyses were made using SAS software, version 8.02 (SAS Institute).

In the treated group (20 males and five females), 15 subjects were treated with peg-IFN alpha-2a and 10 with alpha-2b plus ribavirin (range 800-1200 mg) without achieving an early virological response. The median (IQR) interval between the diagnosis of HCV compensated cirrhosis and the start of therapy was five months (range 3-10), and the median time of anti-HCV therapy was nine months (range 5-12).

Liver histology showing liver cirrhosis was available for 23 treated and 21 untreated patients. Cirrhosis was established by clinical,biochemi-

cal and ultrasonographic criteria in the remaining thrombocytopenic patients. The cirrhosis was classified as Child A in 19 and Child B in six patients in each group (Child-Pugh score 7 in all patients).

The HCV genotype distribution was similar among the treated and untreated patients (1=11 *vs* 6, 3a = 7 *vs* 10, 4 = 3 *vs* 2, not done = 4 *vs* 7; p=NS), as was the distribution of the CDC stage classification (A=17 *vs* 16, B=3 *vs* 3; C=5 *vs* 6; p=NS). In terms of HAART, one treated patient was antiretroviral naive, whereas PI-, NNRTI- and NRTI-based regimens were administered to respectively 8 *vs* 5, 3 *vs* 4 and 11 *vs* 11 patients (p=NS); treatment had been interrupted in three treated and five untreated subjects. The severity of esophageal varices was also uniformly distributed (no varices: 11 *vs* 9; F1: 8 *vs* 11; F2/F3: 6 *vs* 5; p= 0.75). The only laboratory parameters that were statistically different between the two groups were ALT (treated 151 U/L [119-193] vs untreated 98 U/L [76-194] p=0.01) and nadir CD4 counts (treated 216 [117-260] vs untreated 135 [75-229] p=0.05); demographics, other immunovirological and ematobiochemical values were similar.

Four treated (16%) and 13 untreated patients (52%) experienced clinical events (p=0.02), with death due to liver disease occurring in four of the 13 untreated patients (31%): three Child A and one Child B, three of whom were not being treated for HIV at the time of death.

The patients were followed up for an overall total of 116 PYFU, with a median follow-up time of 54 months (IQR: 34-89).

During this time, the treated and untreated patients respectively developed five and 33 events classified by the experts as being related to cirrhosis.

Despite the broad 95% confidence intervals, there was a large difference in the CP rates assessed on the basis of various liver- or HIV-related factors: the patients treated with interferon had a CP rate of 7.7 per 100 PYFU (95% CI: 1.8-33.1) for a total of 65 PYFU, whereas those not treated with interferon had a CP rate of 65.1 per 100 PYFU (95% CI: 4.4-964.8) for a total of 51 PYFU. Among the other HIV and HCV parameters, there were also big differences in relation to nadir CD4 counts (a CP rate of 13.4 per 100 PYFU [95% CI: 0.16-1159] for a total of 59 PYFU at counts of >200/µL, and 55.2 per 100 PYFU [95% CI 5.57-547.3] for a total of 54 PYFU at counts of ≤200 µL); alkaline phosphatase (12.8 per 100 PYFU [95% CI: 2.62-62.2] for a total of 78 PYFU at normal values, and 72.6 per 100 PYFU [95% CI: 4.99-1054] for a total of 37 PYFU at altered values); hemoglobin (25 per 100 PYFU [95% CI: 0.91-690.9] for a total of 100 PYFU at normal values, and 80.9 per 100 PYFU [95% CI: 9.41-695.3] for a total of 16 PYFU at altered values); platelets (2.94 per 100 PYFU [95% CI: 0.41-20.8] for a total of 34 PYFU at normal values, and 45.2 per 100 PYFU [95% CI: 4.59-445.2] for a total of 82 PYFU at altered values); and albumin (24.3 per 100 PYFU [95% CI: 7.43-79.7] for a total of 53 PYFU at normal values, and 65.2 per 100 PYFU [95% CI: 0.39-11159] for a total of 26 PYFU at altered values).

A univariate Poisson regression analysis was used to estimate the significant risks of CP (Table 1). The estimated probability of CP differed between the two groups (p=0.006) (Figure 1). The median time to CP was 25 months in the untreated group, with 25% (Q1) of the patients progressing within six months; among the treated patients, 25% (Q1) of the patients progressed within 49 months, but no median time to progression can be estimated because only 16% of the patients progressed.

The fitting of a multivariable Poisson regression model showed that HCV treatment, HIV-RNA and alkaline phosphatase were independent predictors of CP (Table 1). In particular, treatment with interferon was strongly associated with a significant 97% reduction in the risk of CP (adjusted RR = 0.03; 95% CI: 0.002-0.512; p=0.016); altered ALP values led to a significantly higher risk than normal values (adjusted RR = 25.5; 95% CI: 2.02-320.8; p=0.012); and positive HIV viremia was also a strong predictor of CP (adjusted RR = 35.98; 95% CI: 1,594-812; p=0.024). There was no difference in the results when the synthesis variable (pseudocholinesterases and/or albumin) was included instead of albumin in another multivariable model (data not shown), thus confirming that HCV treatment, HIV-RNA and alkaline phosphatase were the only independent predictors of CP.

As there is currently no effective treatment for the management of HIV/HCV co-infected cir-

TABLE 1 - *Relative CP rates after fitting Poisson's regression model.*

Factor	*Crude RR (95% CI)*	*P*	*Adjusted RR (95% CI)*	*p*
HIV-RNA				
Negative	1.00		1.00	
Positive	0.71 (0.16-3.21)	0.654	35.98 (1.594-812.0)	0.024
Nadir CD4 l				
>200	1.00		1.00	
≤200	4.1 (0.86-19.47)	0.075	0.87 (0.10-7.13)	0.888
HCV treatment				
No	1.00		1.00	
Yes	0.12 (0.02-0.70)	0.019	0.03 (0.002-0.512)	0.016
ALP				
Normal	1.00		1.00	
Altered	5.68 (1.39-23.2)	0.015	25.5 (2.02-320.8)	0.012
Hemoglobin				
Normal	1.00		1.00	
Altered	3.23 (0.84-12.44)	0.088	1.27 (0.1-16.34)	0.857
PLT				
Normal	1.00		1.00	
Altered	15.39 (0.31-762.8)	0.17	6.77 (0.09-518.5)	0.390
Total bilirubin				
Normal	1.00		1.00	
Altered	2.26 (0.59-8.63)	0.232	1.48 (0.18-12.09)	0.712
ALT				
Normal	1.00		1.00	
Altered	1.23 (0.23-6.68)	0.809	0.07 (0.003-1.46)	0.086
PT				
Normal	1.00		1.00	
Altered	1.10 (0.26-4.74)	0.897	0.15 (0.01-2.24)	0.169
Albumin (*)				
Normal	1.00		1.00	
Altered	2.68 (0.58-12.4)	0.208	0.86 (0.12-6.33)	0.884

rhotic patients who do not respond to anti-HCV drugs, data concerning the clinical effects of therapy on the progression of cirrhosis may be useful in guiding future strategies. The aim of this study was therefore to evaluate the clinical impact of peg-IFN and ribavirin on the development of cirrhosis-related complications in patients failing to respond to anti-HCV drugs.

In the HIV/HCV co-infected population, the highest rates of CP have been described among the patients with CD4 counts of <200 cells/μL (Benhamou, Y. *et al.*, 1999; Puoti, M. *et al.*, 2001). The patients were quite homogeneous in terms of baseline characteristics, follow-up and treatment; only baseline serum ALT levels and nadir CD4 counts differed between the groups treated or not for HCV. All of our studied patients started with a diagnosis of cirrhosis and a similar median CD4 count, but the baseline difference in nadir CD4 counts between the two groups means that we cannot exclude its effect on the progression of cirrhosis or HIV infection in the untreated patients; however this variable did not prove to be an independent predictor of CP at multivariable analysis.

Multivariate analysis indicated that only the

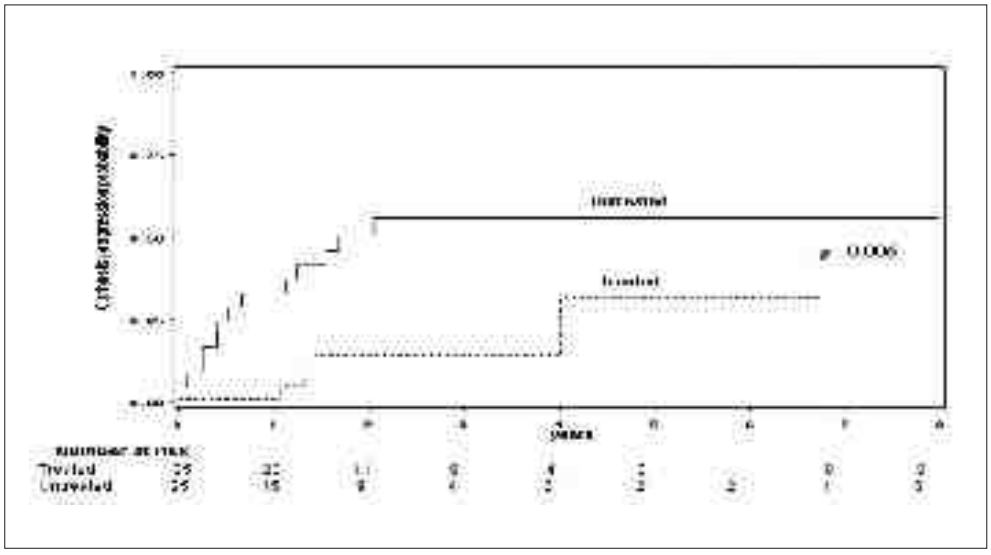

FIGURE 1 - *Estimated probability of cirrhosis progression in HIV/HCV co-infected cirrhotic patients not responding to peg-IFN plus ribavirin vs untreated patients.*

absence of anti-HCV treatment, positive HIV viremia and abnormal alkaline phosphatase levels were significantly associated with the occurrence of liver-related events.

It is worth noting that, in our experience, HCV treatment in non-responders was associated with a significant delay in CP, thus potentially allowing patients to survive longer while awaiting new anti-HCV drugs. However, given the retrospective nature of this analysis and the small sample size, the results must not be over-interpreted.

In patients with HCV infection alone, the results of published studies evaluating the effect of IFN therapy in preventing the complications of cirrhosis and improving survival are controversial. Valla *et al*. and the retrospective, multicentre Eurohep analysis found that it was not associated with any improvement in survival (Valla, D.C. *et al.*, 1999; Fattovich, G. *et al.*, 1997) but other reports suggest that it may be clinically beneficial in cirrhotic patients (Niederau, C. *et al.*, 1998; Benvegnù, L. *et al.*, 1998; Gramenzi, A. *et al*., 2001). In all of the studies showing a clinical benefit, the effect of IFN therapy on CP was related to a sustained virological response, the cumulative IFN dose and the timing of the therapy.

No other therapy is currently approved by the US Food and Drug Administration for HIV/HCV co-infected patients failing on peg-IFN and ribavirin. Maintenance IFN therapy with the goal of preventing disease progression rather than viral eradication seems to offer an option for HCV treatment failures with advanced disease, allowing them to await the introduction of new anti-HCV drugs, such as the small molecule inhibitor of various HCV enzymes.

One important aspect of our study regards HIV-RNA positivity as an independent factor in CP, which suggests that untreated patients or those who are resistant to an ongoing antiretroviral regimen (with detectable viremia during therapy) are more prone to develop cirrhosis-related clinical complications. It is worth noting that three of our four patients who died of end-stage liver disease had not been treated with anti-HIV drugs for at least six months before their deaths. This finding, which is perfectly in line with the high level of mortality due to end-stage liver disease described in untreated patients or patients unsuccessfully treated with HAART, suggests that HAART should not be stopped or reduced in cirrhotic HCV patients because the survival benefit seems to outweigh the associated risk of severe hepatotoxicity (Rockstroh, J. *et al.*, 2005; Qurishi, N. *et al.*, 2003).

In conclusion, it is encouraging to note that peg-IFN therapy seems to be able to slow down the rate of cirrhosis progression in HIV/HCV co-infected patients not only in responders, but also in non-responders to peg-IFN and ribavirin therapy, because this effect may allow some patients to await more effective future therapies.

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