

Effect of protease inhibitors and non-nucleoside reverse transcriptase inhibitors on liver histology in HIV-HCV co-infection: analysis of patients enrolled in the AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT)

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INTRODUCTION

In patients with human immunodeficiency virus (HIV), co-infection with hepatitis C virus (HCV) is common and progression of HCV-related liver fibrosis is accelerated. Mortality associated with HIV has decreased dramatically with the introduction of highly active antiretroviral therapy (HAART). However, the impact of HAART, including protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors (NRTIs), and non-NRTIs (NNRTIs), on the spectrum of HCV-related liver disease remains unclear.

Although early data suggested that PIs are associated with a slower progression of liver fibrosis,^[1] more recent data suggest no significant difference in liver histology in patients on PIs or NNRTIs, compared with those not receiving such treatment.^[2] These studies, however, included a relatively small number of patients. The recent AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT)^[3] is the largest study of peginterferon therapy ever conducted in patients with HIV-HCV co-infection, involving almost 900 patients. This study provides a large patient database in which the impact of HAART on liver disease can be explored further.

OBJECTIVE

The aim of this analysis was to determine the impact of PIs and/or NNRTIs on liver histology in HIV-HCV co-infected patients taking part in APRICOT.

METHODS

HIV-infected patients aged ≥18 years, with detectable anti-HCV antibodies in serum, detectable HCV RNA (>600 IU/mL) and compensated liver disease were eligible for inclusion in the study. The presence of HIV type 1 disease was confirmed by detection of anti-HIV-1 antibodies or HIV-1 RNA in serum (AMPLICOR[®] HIV-1 Monitor Test, version 1.5). Patients were required to either have been receiving stable antiretroviral therapy for at least 6 weeks before study entry, with no changes expected for the first 8 weeks of the study, or not to have received any antiretroviral therapy for at least 8 weeks before randomization and to be able to delay the initiation of antiretroviral therapy for at least 6 weeks.

Eligible patients were randomized to receive peginterferon alfa-2a (40KD) (PEGASYS[®]) 180 µg/week plus ribavirin (COPEGUS[®]) 400 mg bid, peginterferon alfa-2a (40KD) 180 µg/week plus placebo bid, or interferon alfa-2a (Roferon[®]-A, 3 million IU tiw) plus ribavirin 400 mg bid for 48 weeks. A baseline liver biopsy was performed up to 15 months prior to the patient entering the study, and was scored by local pathologists using the Ishak modified Histologic Activity Index (HAI) system^[4] (Table 1). For the purpose of this analysis, advanced liver histology was defined as an Ishak fibrosis score of 4–6. A previously published report from this study contained liver histology data that were restricted to patients with cirrhosis.^[5]

A retrospective analysis of liver histology was performed in patients with baseline liver biopsy data available whose pre-biopsy HAART regimen within 2 months preceding the biopsy was known.

In this analysis, patients were grouped according to their HAART regimen prior to liver biopsy: those using a PI, those using an NNRTI, those using both a PI and NNRTI, and those who were receiving neither a PI nor an NNRTI. The prevalence of advanced fibrosis in each subgroup was determined and statistical comparisons between the groups performed using a chi-square test. An analysis was also performed to compare the demographic and disease characteristics of patients according to their fibrosis status

Table 1. Assessment of liver histology using Ishak modified HAI score^[4]

	Necroinflammation: 0–18	Fibrosis: 0–6	
Periportal necrosis	0–4	None	0
Confluent necrosis	0–6	Portal (some)	1
Focal necrosis	0–4	Portal (most)	2
Portal inflammation	0–4	Bridging (some)	3
		Bridging (most)	4
		Cirrhosis (incomplete)	5
		Cirrhosis (complete)	6

HAI = histologic activity index.

(Ishak score 0–3 vs Ishak score 4–6). Differences between characteristics of patients in the groups were compared by t-test for continuous variables and chi-square test for categorical variables with a nominal scale. Wilcoxon rank-sum tests were used for ordinal data and continuous variables with strong deviation from the normal distribution.

RESULTS

A total of 868 patients were randomized to receive treatment. Of these, 178 patients had no available information on pre-biopsy HAART and were therefore excluded from this analysis, leaving a total of 690 patients. Of these, 157 patients (23%) had advanced fibrosis (Ishak score 4–6). Three-hundred and twelve patients (45%) were taking PIs, 205 (30%) were taking NNRTIs, 53 (8%) were taking both, and 120 (17%) were taking

Table 2. Demographic and baseline characteristics of patients with pre-biopsy highly active antiretroviral therapy data

	PI	NNRTI	PI + NNRTI	No PI or NNRTI	P value*
No. of patients	312	205	53	120	
Mean age, years ± SD	41 ± 8	40 ± 8	40 ± 6	39 ± 7	NS
Male, %	80	82	89	78	NS
Race, %					NS
Caucasian	77	76	81	83	
Black	11	11	11	11	
Hispanic	13	12	8	4	
Other	0	2	0	2	
Mean weight, kg ± SD	73 ± 13	72 ± 13	74 ± 14	75 ± 14	NS
Mean BMI, ± SD	25 ± 4	24 ± 4	24 ± 4	25 ± 4	NS
Mean HCV RNA × 10 ³ IU/mL, ± SD	6016 ± 6482	5687 ± 6438	6590 ± 7510	5640 ± 6095	NS
HCV genotype 1, %	63	64	51	56	NS
Mean HIV RNA copies/mL ± SD	4797 ± 29401	1754 ± 7513	6102 ± 24480	23558 ± 75481	<0.0001
Patients with detectable HIV RNA, %	32	24	28	79	<0.0001
Mean CD4 cells/mm ³ , ± SD	511 ± 264	541 ± 278	481 ± 243	568 ± 302	NS
Mean CD4%, ± SD	25 ± 9	27 ± 10	23 ± 10	27 ± 10	NS
Mean CD8 cells/mm ³ , ± SD	986 ± 457	926 ± 422	981 ± 460	982 ± 447	NS
Mean ALT, U/L	81 ± 46	93 ± 63	88 ± 41	92 ± 56	NS
Mean HAI total	8.2 ± 3.9	7.8 ± 3.8	7.6 ± 3.2	8.0 ± 3.5	NS
Inflammation score	5.6 ± 2.7	5.4 ± 2.6	5.2 ± 2.3	5.7 ± 2.5	NS

* PI/NNRTI (three groups combined) vs no PI/NNRTI.

ALT = alanine aminotransferase; BMI = body mass index; HAI = histologic activity index; NNRTI = non-nucleoside reverse transcriptase inhibitor; NS = not significant; PI = protease inhibitor.

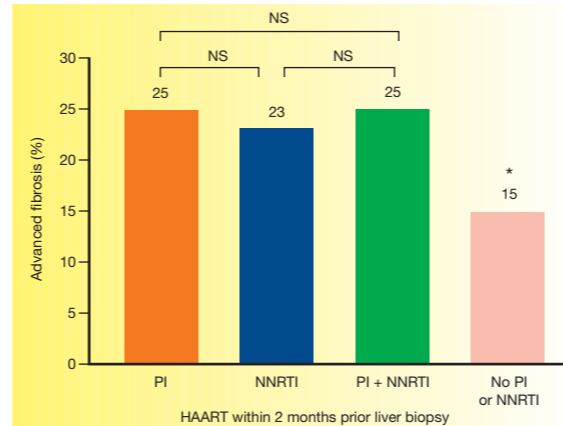


Figure 1. Prevalence of advanced fibrosis among patients receiving a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) alone or in combination or neither treatment. * P=0.026 vs PI/NNRTI (three groups combined); HAART = highly active antiretroviral therapy; NS = not statistically significant.

Table 3. Demographic and baseline characteristics of patients with Ishak 0–3 or Ishak 4–6

	Ishak score 0–3	4–6	P value
No. of patients	533	157	
Mean age, years ± SD	40 ± 7	42 ± 8	<0.0001
Male, %	81	82	NS
Race, %			NS
Caucasian	77	79	
Black	11	8	
Hispanic	10	11	
Other	1	1	
Mean weight, kg ± SD	73 ± 13	74 ± 14	NS
Mean BMI, ± SD	25 ± 4	25 ± 4	NS
Mean HCV RNA × 10 ³ IU/mL ± SD	6133 ± 6763	5166 ± 5379	NS
HCV genotype 1, %	61	62	NS
Mean HIV RNA copies/mL, ± SD	8429 ± 43 212	3019 ± 11 819	NS
Patients with detectable HIV RNA%	38	33	NS
Mean CD4 no. cells/mm ³ , ± SD	532 ± 276	513 ± 267	NS
Mean CD4%, ± SD	26 ± 9	25 ± 10	NS
Mean CD8 no. cells/mm ³ , ± SD	960 ± 441	990 ± 459	NS
Mean ALT (U/L)	87 ± 53	89 ± 56	NS
Mean HAI total	6.8 ± 2.9	12.2 ± 3.3	<0.0001
Inflammation score	5.0 ± 2.2	7.3 ± 3.1	<0.0001

ALT = alanine aminotransferase; BMI = body mass index; HAI = histologic activity index; NS = not significant.

neither. Of those patients not on a PI or NNRTI, 43 (36%) were not receiving any HAART within 2 months prior to liver biopsy. Total exposure to HAART in this patient population (i.e. HAART taken before the 2-month window prior to biopsy) is not known.

Baseline demographics and characteristics

The baseline demographic and disease characteristics of the patients are shown in Table 2. The four groups were well matched for age, race, weight, body mass index, HCV titer, HCV genotype, and mode of infection. However, those patients not receiving a PI or NNRTI were more likely to have detectable serum HIV RNA compared with those on a PI, an NNRTI or both (P<0.0001).

Prevalence of advanced fibrosis

The prevalence of advanced fibrosis was significantly greater among patients receiving a PI, an NNRTI or both in combination (23–25% of patients, depending on regimen) compared with those who were not taking a PI or NNRTI (15%; P=0.026) (Figure 1). There was no significant difference in the prevalence of advanced fibrosis among patients receiving a PI and patients receiving an NNRTI-containing regimen. The prevalence of advanced fibrosis was 19% among patients receiving nevirapine, compared with 23% in patients who did not receive nevirapine. This difference was not statistically significant (P=0.352).

Factors associated with the presence of advanced fibrosis

In general, there were no statistically significant demographic, biochemical, or virological differences between patients with or without advanced fibrosis (Table 3). However, patients with advanced fibrosis were significantly older (mean age 42 years vs 40 years; P<0.0001), compared with patients with an Ishak score of 0–3.

CONCLUSIONS

The results of this analysis of biopsy data from almost 700 patients taking part in APRICOT have confirmed previous findings that advanced fibrosis is common among those co-infected with HIV and HCV. Almost one-quarter of all patients studied had advanced fibrosis.

The prevalence of advanced fibrosis was significantly lower among patients who were not receiving a PI or NNRTI, compared with those who were taking a PI, NNRTI or both, although the effect of other confounding factors could not be excluded. There was, however, no significant differences in liver histology or the incidence of advanced fibrosis among patients receiving a PI compared with those receiving an NNRTI. Thus, for patients with HIV-HCV co-infection, the choice of HAART should be based on the potency and durability of the antiretroviral regimen, with less emphasis on the potential impact on hepatotoxicity or progression of fibrosis. The observation that advanced fibrosis is less common in those patients not taking a PI and/or NNRTI requires further investigation.

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