Histological response to pegIFNα-2a (40KD) plus ribavirin in HIV–hepatitis C virus co-infection

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Objective: Paired liver biopsies from patients enrolled in the multinational AIDS PEGASYS Ribavirin International Co-infection Trial were analysed to investigate a possible correlation between virological and histological responses.

Design and methods: A total of 860 HIV–hepatitis C virus (HCV)-co-infected patients were randomly assigned to receive pegIFNα-2a (40KD) 180 μg/week plus 800 mg daily ribavirin, pegIFNα-2a (40KD) plus placebo or conventional IFNα-2a 3 MIU three times a week plus ribavirin for 48 weeks. Paired biopsies were obtained from 401 patients and scored locally using the Ishak-modified histological activity index (HAI). The second biopsy was obtained, on average, 26 weeks or more after the end of treatment. Histological response was defined as a 2-point or greater reduction in the HAI score.

Results: The histological response rate was significantly higher in patients receiving pegIFNα-2a (40KD) plus ribavirin (57%) than in patients receiving pegIFNα-2a (40KD) plus placebo (39%; $P < 0.017$) or IFNα-2a plus ribavirin (41%; $P = 0.04$). Histological response was correlated with virological response, with the histological response rate ranging from 62 to 74% in patients who achieved a sustained virological response (SVR). Histological response was also seen in 32–43% of patients not achieving an SVR. A higher total HAI score was the only prognostic factor for achieving histological response.

Conclusion: The histological response rate was significantly higher in HIV–HCV-co-infected patients who received pegIFNα-2a (40KD) plus ribavirin than in those receiving pegIFNα-2a (40KD) plus placebo or IFNα-2a plus ribavirin. Histological response was correlated with virological response, although a substantial proportion of patients who did not achieve an SVR experienced histological improvement.

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Introduction

The improved survival of HIV-infected patients seen with effective antiretroviral therapy (ART) has resulted in an increase in the clinical relevance of hepatitis C virus (HCV) co-infection. Liver disease is now a major source of morbidity and mortality in patients with HIV infection [1,2].

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Compared with HCV monoinfection, the progression of HCV-induced liver disease is accelerated in patients co-infected with HIV and HCV [3,4]. The urgency for treatment is thus greater in patients with HIV–HCV co-infection than in patients with HCV monoinfection [1,5].

Liver histology often improves when HCV replication is suppressed in monoinfected patients with chronic hepatitis C, even in the absence of viral eradication [6,7]. Until recently, limited data have been available concerning the effect of interferon-based therapy on histological outcomes in patients co-infected with HIV and HCV.

The AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT) was the first large, randomized, multinational trial to examine the efficacy of pegylated interferon plus ribavirin in patients with HIV–HCV co-infection [8]. In APRICOT, the overall sustained virological response (SVR) rate at the end of follow-up was significantly greater in pegIFNα-2a (40KD) plus ribavirin recipients (40%) than in pegIFNα-2a (40KD) plus placebo recipients (20%; $P < 0.001$) or conventional IFNα-2a plus ribavirin recipients (12%; $P < 0.001$).

The objective of this analysis was to investigate the histological response to treatment and the possible correlation between virological and histological responses in patients enrolled in APRICOT. In addition, we also aimed to explore prognostic factors for an histological response in patients who received the combination of pegIFNα-2a (40KD) plus ribavirin.

Methods

Patient characteristics

Patients eligible for APRICOT were HCV treatment-naive adults aged over 18 years with HIV–HCV co-infection [8]. They were required to have quantifiable serum HCV-RNA levels by polymerase chain reaction assay (Cobas Amplicor HCV Monitor Test, v2.0; Roche Diagnostics, Pleasanton, California, USA; limit of quantitation 600 IU/ml), elevated serum alanine aminotransferase activity, compensated liver disease and findings on a liver biopsy consistent with the diagnosis of chronic hepatitis C. Eligible participants had a CD4 cell count of 200 cells/μl or greater (or a CD4 cell count of 100–200 cells/μl if the serum HIV-1-RNA level was < 5000 copies/ml). Patients were required to have stable HIV disease, which was defined as the absence of active opportunistic infections or malignancy requiring acute systemic therapy, and either to be receiving stable ART or no ART. An ART regimen was considered to be stable if no changes were expected during the first 8 weeks of study treatment. Patients who were not receiving ART must not have received ART during the 8 weeks before random selection, and were required not to have plans to start ART during the first 6 weeks of study treatment. The complete inclusion and exclusion criteria are published elsewhere [8].

Study design

Patients were randomly assigned to 48 weeks of treatment with subcutaneous pegIFNα-2a (40KD) (Pegasys; Roche, Basel, Switzerland) 180 μg once a week plus either oral ribavirin (Copegus; Roche) 400 mg twice a day or placebo, or subcutaneous IFNα-2a (Roferon-A; Roche) 3 MIU three times a week plus ribavirin [8]. Patients were to be followed for 24 weeks after the 48-week treatment period. The assignment to ribavirin or placebo was double-blind in the pegIFNα-2a (40KD) treatment arms. All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Histological outcome measures

Liver biopsies were obtained 15 months or less before baseline and at the end of follow-up (≥ 56 days posttreatment). Biopsies were assessed by the local pathologists at each site as they were obtained, in accordance with the manner in which biopsies are assessed in clinical practice (i.e. no attempt was made to mask the pathological evaluations at local study sites). If the surgical procedure was contraindicated (e.g. in patients with hemophilia and those allergic to anesthesics), the requirement for a liver biopsy was waived. The sponsor conducted a retrospective blinded central reading of all available paired biopsies in order to validate the histological assessments of the local pathologists; this was performed by Dr Sugantha Govindarajan of the Liver Research Laboratory, Downey, California.

Biopsies were scored using the Ishak-modified histological activity index (HAI) scoring system [9]. The necroinflammatory grade is scored from 0 (no necroinflammation) to a maximum of 18, and the staging of fibrosis is based on scores that range from 0 (no fibrosis) to 6 (cirrhosis, probable or definite) [9].

In this analysis 'bridging fibrosis' includes all patients assigned a fibrosis stage of 5 and those who were assigned stage 4, but had nodules or more than three bridges. Therefore, 17 patients with stage 4 fibrosis and more than three bridges were included in the group described as having bridging fibrosis/cirrhosis ($n = 134$) among the 860 patients in the overall study population treated.

An histological response was defined as a 2-point or greater reduction from baseline in the Ishak-modified HAI score. No change was defined as a change in HAI score of +1, −1, or 0, and worsening was defined as an increase in the HAI score of 2 or more points.

SVR (the primary efficacy endpoint in APRICOT) was defined as undetectable serum HCV RNA by qualitative

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polymerase chain reaction assay (Cobas Amplicor HCV Monitor Test, v2.0, limit of detection < 50 IU/ml) at the end of the 24-week untreated follow-up period (study week 72).

Statistical analysis

The histological analysis presented in this paper is based on data from all patients who had paired pretreatment and posttreatment biopsies. No selection criteria were used for the histological analysis beyond the original inclusion and exclusion criteria.

For the comparison of histological response rates, pairwise comparisons were tested using the Cochran–Mantel–Haenszel test, adjusted for geographical region, HCV genotype, and baseline CD4 cell count. Changes in total HAI scores, necroinflammatory scores and fibrosis scores were analysed by Wilcoxon signed rank test adjusted for geographical region, HCV genotype, and baseline CD4 cell count. Two-tailed *P* values less than 0.05 were deemed to be statistically significant.

Stepwise multiple logistic regression analysis was used to explore the prognostic factors for an histological response in patients receiving pegIFNα-2a (40KD) plus ribavirin. In the stepwise model building process, a variable was added to the model if the adjusted chi-square statistic was significant at the 0.15 level, and a variable was deleted from the model if the Wald chi-square statistic was not significant at the 0.1 level. The following baseline disease and demographic factors were considered for entry into the model: geographical region, age, sex (male versus female), race (Caucasian versus non-Caucasian), body mass index, $\log_{10}$ pretreatment serum HCV-RNA titer, total HAI score at baseline, qualifying alanine aminotransferase quotient, HCV genotype (1 versus non-1), CD4 cell count, use of ART (yes versus no) and histological diagnosis (cirrhosis versus no cirrhosis). Odds ratios (OR) and 95% confidence intervals (CI) were estimated for the independent prognostic factors.

Results

A total of 868 patients were randomly selected in APRICOT, 860 of whom received at least one dose of study drug (285 patients received conventional IFNα-2a plus ribavirin, 286 received pegIFNα-2a (40KD) plus placebo, and 289 received pegIFNα-2a (40KD) plus ribavirin). Paired biopsies were obtained from 401 treated patients (47%) at 74 participating centers in 18 countries. The number of patients with paired biopsies in each of the treatment groups was approximately the same (132 recipients of conventional IFNα2-a plus ribavirin, 134 recipients of pegIFNα-2a (40KD) plus placebo, and 135 recipients of pegIFNα-2a (40KD) plus ribavirin). Of these, 97, 96, and 90 paired biopsy specimens from the corresponding treatment groups were submitted for centralized reading.

The second biopsy was obtained, on average, 26 weeks or more after the end of treatment.

The baseline characteristics of patients with paired biopsy specimens were similar across the three treatment groups (Table 1). Importantly, the baseline demographic, disease and histological characteristics of the subgroup of patients with paired biopsies were very similar to those of the overall APRICOT population.

Two-thirds of paired biopsies (263 of 401, 66%) were obtained from patients who did not achieve an SVR, although the proportion varied in inverse proportion to the overall SVR rates in the three treatment groups [105 of 132 (80%) recipients of conventional IFNα-2a plus ribavirin, 97 of 134 (72%) recipients of pegIFNα-2a (40KD) plus placebo, and 61 of 135 (45%) recipients of pegIFNα-2a (40KD) plus ribavirin].

Histological response

The overall histological response rate was significantly higher in recipients of pegIFNα-2a (40KD) plus ribavirin (57%) than in recipients of either pegIFNα-2a (40KD) plus placebo (39%; $P < 0.017$) or conventional IFNα-2a plus ribavirin (41%; $P = 0.04$) (Table 2). No change in HAI score was seen in 30–39% of patients across the three treatment groups. A worsening of the HAI score was seen in 20% of conventional IFNα-2a plus ribavirin recipients, 27% of pegIFNα-2a (40KD) plus placebo recipients and 13% of pegIFNα-2a (40KD) plus ribavirin recipients.

The results in HCV genotype 1 patients were similar to those in the overall population. An histological response was obtained in 55% (41 of 75) of genotype 1 patients treated with peginterferon pegIFNα-2a (40KD) plus ribavirin, 37% (32 of 87) of those treated with pegIFNα-2a (40KD) plus placebo and 35% (26 of 75) of those treated with conventional IFNα-2a plus ribavirin. A worsening of HAI scores was documented in 23% (17 of 75) of genotype 1 patients treated with conventional IFNα-2a plus ribavirin, 31% (27 of 87) of those treated with pegIFNα-2a (40KD) plus placebo and 15% (11 of 75) of those treated with pegIFNα-2a (40KD) plus ribavirin.

Reductions from baseline in the total HAI score and the necroinflammatory grade were substantially greater with pegIFNα-2a (40KD) plus ribavirin than with pegIFNα-2a (40KD) plus placebo or IFNα-2a plus ribavirin (Fig. 1). The mean fibrosis stage improved in recipients of pegIFNα-2a (40KD) plus ribavirin, and the extent of improvement was significantly greater than that seen with pegIFNα-2a (40KD) plus placebo ($P = 0.006$, Fig. 1).

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Table 1. Comparison of baseline characteristics in the overall population with those participating in the histological analysis.

Characteristic	IFNα-2a + ribavirin		PegIFNα-2a (40KD) + placebo		PegIFNα-2a (40KD) + ribavirin	
Patients	All ($n = 285$)	Paired biopsy ($n = 132$)	All ($n = 286$)	Paired biopsy ($n = 134$)	All ($n = 289$)	Paired biopsy ($n = 135$)
Male, *n* (%)	231 (81)	109 (83)	234 (82)	114 (85)	232 (80)	110 (81)
Caucasian, *n* (%)	223 (78)	104 (79)	225 (79)	101 (75)	231 (80)	104 (77)
Age (years)	40.1 ± 7.6	40.9 ± 7.4	40.0 ± 7.4	40.2 ± 7.0	39.7 ± 7.9	39.9 ± 8.3
Body mass index (kg/m^2)	24.9 ± 4.2	24.8 ± 3.4	24.7 ± 3.8	25.0 ± 3.9	24.2 ± 4.1	24.1 ± 3.8
HCV genotype, *n* (%)						
1	171 (60)	75 (57)	175 (61)	87 (65)	176 (61)	75 (56)
2	14 (5)	8 (6)	17 (6)	9 (7)	13 (4)	6 (4)
3	75 (26)	38 (29)	73 (26)	31 (23)	82 (28)	44 (33)
4	24 (8)	11 (8)	20 (7)	6 (4)	16 (6)	10 (7)
Other/unknown	1 (< 1)	0	1 (< 1)	1 (< 1)	2 (1)	0
Total histological activity index score	8.0 ± 3.8	8.0 ± 3.7	7.9 ± 3.7	8.3 ± 3.3	8.0 ± 3.8	8.1 ± 3.6
Necroinflammation (grade)	5.6 ± 2.7	5.5 ± 2.8	5.5 ± 2.6	5.8 ± 2.4	5.6 ± 2.7	5.5 ± 2.4
Fibrosis (stage)	2.4 ± 1.6	2.5 ± 1.6	2.4 ± 1.7	2.5 ± 1.5	2.4 ± 1.7	2.5 ± 1.7
Bridging fibrosis or cirrhosis, *n* (%)	45 (16)	22 (17)	45 (16)	20 (15)	44 (15)	22 (16)
Receiving ART, *n* (%)	240 (84)	113 (86)	243 (85)	112 (84)	244 (84)	113 (84)
HIV RNA titer (copies/ml)	8426 ± 46 515	5108 ± 18 801	8278 ± 39 576	12 356 ± 55 317	10 097 ± 48 322	8846 ± 37 275
Undetectable HIV RNA (< 50 copies/ml), *n* (%)	170 (60)	81 (61)	171 (60)	81 (60)	173 (60)	78 (58)
CD4 cells/μl	542 ± 270	557 ± 248	530 ± 265	512 ± 239	520 ± 277	484 ± 206
HCV RNA × 10^6 IU/ml	5.2 ± 6.0	5.3 ± 6.6	6.4 ± 6.4	6.6 ± 6.6	5.6 ± 6.4	5.9 ± 6.5

ART, Antiretroviral therapy; HCV, hepatitis C virus. Plus–minus values are means ± SD.

Histological and virological responses were correlated. The majority of patients with an SVR also had an histological response (Fig. 2). In patients treated with pegIFNα-2a (40KD) plus ribavirin who had an SVR, 69% also had an histological response, but only 5% had worsening histology. Histological responses were also seen in patients who did not achieve an SVR; in these patients, the highest histological response rate (43%) occurred with pegIFNα-2a (40KD) plus ribavirin (Fig. 2). Approximately one-third of patients without a documented virological

Table 2. Histological response in patients with paired liver biopsies.

	IFNα-2a + ribavirin	PegIFNα-2a (40KD) + placebo	PegIFNα-2a (40KD) + ribavirin
All patients with paired biopsies			
N	132	134	135
No. of centers submitting paired biopsies	56	57	54
Mean time of second biopsy in weeks ± SD relative to end of treatment	26 ± 10	26 ± 6	27 ± 9
Median time of second biopsy relative to end of treatment (range)	25 (8–67)	25 (9–53)	25 (8–69)
Histological response, *n* (%)	54 (41)	52 (39)	77 (57)*,†
Histological non-response, *n* (%)	78 (59)	82 (61)	58 (43)
No change, *n* (%)	51 (39)	46 (34)	40 (30)
Worsening, *n* (%)	27 (20)	36 (27)	18 (13)
Patients with paired biopsies who did not have a documented virological response at any time during treatment or follow-up			
N	85	60	34
Histological response, *n* (%)	27 (32)	19 (32)	12 (35)
Histological non-response, *n* (%)	58 (68)	41 (68)	22 (65)
No change, *n* (%)	37 (44)	24 (40)	13 (38)
Worsening, *n* (%)	21 (25)	17 (28)	9 (26)
Patients with paired biopsies and a histological diagnosis of bridging fibrosis or cirrhosis at baseline			
N	22	20	22
Histological response, *n* (%)	10 (45)	7 (35)	15 (68)
Histological non-response, *n* (%)	12 (55)	13 (65)	7 (32)
No change, *n* (%)	7 (32)	8 (40)	6 (27)
Worsening, *n* (%)	5 (23)	5 (25)	1 (5)
Histological response in patients with an SVR	4/4	2/5	8/10
Histological response in patients without an SVR	6/18	5/15	7/12

SVR, Sustained virological response.
*$P = 0.04$ versus IFNα-2a plus ribavirin;
†$P < 0.017$ versus pegIFNα-2a (40KD) plus placebo.

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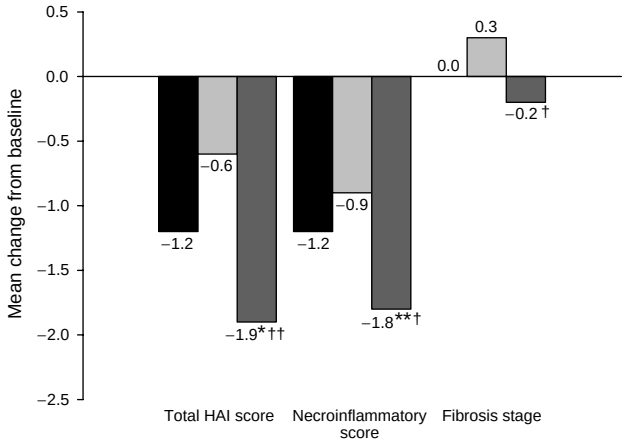

Fig. 1. Mean change from baseline in total histological activity index score, necroinflammatory score and fibrosis stage (using the Ishak-modified scoring system). HAI, Histological activity index. ■ IFNα-2a plus ribavirin ($n=132$); □ pegIFNα-2a (40KD) plus placebo ($n=134$); ■ pegIFNα-2a (40KD) plus ribavirin ($n=135$). $^{*}P=0.015$, $^{**}P=0.006$ versus IFNα-2a plus ribavirin; $^{\dagger}P=0.006$, $^{\dagger\dagger}P=0.001$ versus pegIFNα-2a (40KD) plus placebo.

response at any time during treatment (i.e. at weeks 4, 12, 24, 36 and 48), had an histological response (Table 2).

This pattern was also apparent when only genotype 1 patients were considered. Among patients treated with pegIFNα-2a (40KD) plus ribavirin the histological response rate was 64% (21 of 33) in patients with an SVR and 48% (20 of 42) in patients without an SVR. Among genotype 1 patients who did not have a virological response at any time during treatment, 44% (11 of 25) of those treated with pegIFNα-2a (40KD) plus ribavirin were histological responders.

When the results of the centralized reading of biopsies were compared with those from local readings for patients

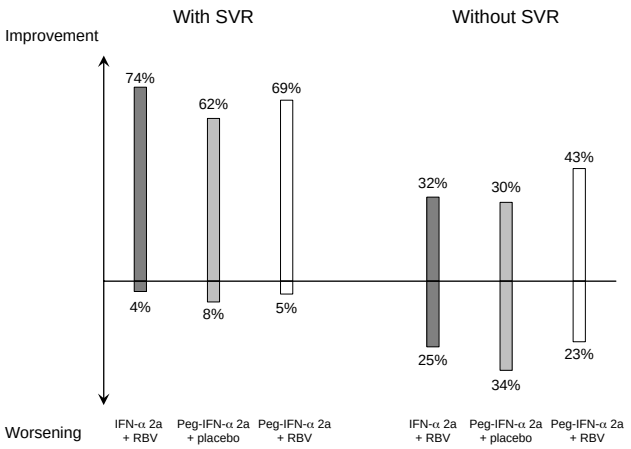

Fig. 2. Histological response rate in patients with (left) and without (right) sustained virological responses. RBV, Ribavirin; SVR, sustained virological response.

treated with pegIFNα-2a (40KD) plus ribavirin, the baseline total HAI scores and changes in necroinflammatory scores assigned by the central pathologist were slightly higher than those assigned by the local pathologists, although scores assigned for the change in fibrosis stage were identical (Table 3). Importantly, the overall histological response rate assigned by the central reading of biopsies (56%) was almost identical to that produced by the local reading of biopsies (57%).

Histological outcomes in patients with bridging fibrosis or cirrhosis

Paired biopsies were obtained for 64 of 134 patients with a histological diagnosis of bridging fibrosis or cirrhosis at baseline (Table 2). In general, the results in these patients mirrored those in the overall population with paired biopsies. Histological response rates were slightly higher in patients with bridging fibrosis or cirrhosis compared with the overall population (Table 2).

The highest histological response rate was obtained in patients treated with pegIFNα-2a (40KD) plus ribavirin (15 of 22, 68%). Of the 22 patients with paired liver biopsies in this group, 10 had SVR, eight of whom had both an histological and a virological response. Of the 12 remaining patients in this group who did not have an SVR, seven (58%) had an histological response.

Baseline predictors of histological response in patients treated with pegIFNα-2a (40KD) plus ribavirin

In the final multiple logistic regression model of histological response in patients receiving pegIFNα-2a (40KD) plus ribavirin only a higher total HAI score at baseline was predictive of an histological response. The odds of achieving an histological response increased on average by factor 1.27 for a one unit increase in the total

Table 3. Comparison of histological outcomes based on central and local assessment of biopsies in patients treated with pegIFNα-2a (40KD) plus ribavirin.

Assessment	Local	Central
Paired biopsies, *N*	135	90
Mean baseline histological activity index score	8.1	9.5
Mean change in histological activity index score (baseline to end of follow-up)		
Total	−1.9	−2.3
Necroinflammation	−1.8	−2.1
Fibrosis	−0.2	−0.2
Histological response, *n* (%)	77 (57)	50 (56)
Outcome in patients with an SVR, *n* (%)		
Histological response	51 (69)	39 (78)
No change	19 (26)	9 (18)
Worsening	4 (5)	2 (4)
Outcome in patients without an SVR, *n* (%)		
Histological response	26 (43)	11 (28)
No change	21 (34)	19 (48)
Worsening	14 (23)	10 (25)

SVR, Sustained virological response.

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HAI score (OR 1.27, 95% CI 1.12–1.43; $P=0.0001$). The total HAI score was also the main predictive factor in the two other treatment groups. In the logistic regression model with two independent factors (treatment group and total HAI score at baseline), the histological response rate in patients treated with pegIFNα-2a (40KD) plus ribavirin was statistically significantly higher compared with either pegIFNα-2a (40KD) plus placebo (OR 2.48, 95% CI 1.47–4.19; $P=0.0007$) or IFNα-2a plus ribavirin (OR 2.08, 95% CI 1.23–3.51; $P=0.0063$), whereas there was no significant difference between IFNα-2a plus ribavirin and pegIFNα-2a (40KD) plus placebo ($P=0.5078$).

Discussion

The results of this analysis demonstrate that the pattern of histological response was similar to the pattern of virological response in APRICOT [8]. Patients who received pegIFNα-2a (40KD) plus ribavirin experience significantly higher histological response rates than patients who received pegIFNα-2a (40KD) plus placebo or IFNα-2a plus ribavirin.

Liver biopsies were not obtained from all patients enrolled in APRICOT; however, the relative number obtained across the three treatment groups was similar. The number of patients with posttreatment biopsies was low for two primary reasons: (1) a large proportion of patients refused to undergo a second liver biopsy; and (2) patients who prematurely discontinued treatment and did not have a virological response at the time of discontinuation were not required to return for assessments beyond 12 weeks postdiscontinuation, and thus generally did not return for the week 72 assessment or posttreatment liver biopsy.

Histological response was correlated with SVR. Of the patients who received pegIFNα-2a (40KD) plus ribavirin and who achieved an SVR, over two-thirds also experienced an histological response. The results were similar across the three treatment arms in the study, although significantly more patients achieved an SVR after treatment with pegIFNα-2a (40KD) plus ribavirin. The number of patients who obtained a histological benefit was thus greatest in this group. Whereas the majority of posttreatment biopsies were taken approximately 6 months after the end of treatment, it may be that further improvement will occur over longer durations in patients in whom HCV has been eradicated. One caveat of studies such as ours, examining changes in fibrosis, is the short time between biopsies. Because fibrotic improvement is a slow process, it may be that to assess the benefit of treatment on fibrosis, it may be more appropriate to repeat liver biopsies 2–3 years later [6]. Although histological response rates were lower in patients who did not achieve an SVR, a substantial proportion of pegIFNα-2a (40KD) plus ribavirin recipients who did not achieve an SVR did achieve an histological response (43%). It should also be noted that histological responses were obtained in approximately one-third of patients who did not have a virological response at any time during treatment (i.e. true virological non-responders). Presumably the extent of benefit would be similar or somewhat greater in patients who had a temporary or partial virological response. Although the long-term histological benefits to patients who did not have an SVR require further investigation, these findings demonstrate that patients with HIV–HCV co-infection benefit from therapy, even in the absence of an SVR.

These findings are also applicable to those with difficult-to-treat HCV genotypes (e.g. HCV genotype 1) or advanced liver disease in whom there is a lower probability of HCV clearance. For patients infected with HCV genotype 1, an histological response was observed in 55% of those treated with pegIFNα-2a (40KD) plus ribavirin. Furthermore, almost half of the genotype 1 patients who failed to achieve an SVR with this combination achieved an histological response. Histological outcomes in the small subset of patients with a diagnosis of bridging fibrosis or cirrhosis were similar to those in the overall population. This is particularly important given the more rapid progression of liver disease in patients with HIV–HCV co-infection.

The results of the APRICOT histological analysis are in general agreement with the results of studies showing the beneficial effect of pegylated interferon (with or without ribavirin) on liver histology in patients with chronic hepatitis C without HIV infection. A meta-analysis of individual patient data found that pegIFNα-2a (40KD) monotherapy reduced fibrosis to a significantly greater extent than conventional interferon monotherapy [6]. Moreover, treatment with pegIFNα-2b (12KD) with or without ribavirin was associated with a significant reduction from baseline in the rate of fibrosis progression in a pooled analysis of individual patient data [7]. The effect of pegIFNα-2b (12KD) on liver histology was correlated with the virological response, although an improvement in liver fibrosis was seen in patients without a virological response in one analysis [7], but not in the other, although this finding was most likely attributable to methodological differences between the analyses [6]. Interestingly, the addition of ribavirin to each of the pegylated interferons was associated with an increase in the histological benefits. This clearly illustrates that ribavirin plays some role in histological improvement. Further studies are required to investigate the mechanism of this.

Limited data are available on the impact of pegylated interferons on liver histology in patients with HIV–HCV co-infection. The Adult AIDS Clinical Trials Group (ACTG) A5071 trial also examined the effect of pegIFNα-2a (40KD) plus ribavirin on liver histology

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in patients with HIV–HCV co-infection [10]. The APRICOT and the ACTG A5071 trials differ in terms of certain design features and patient characteristics. For example, the ACTG A5071 trial included patients with both elevated and normal alanine aminotransferase levels, had greater proportions of African-American and HCV genotype 1-infected patients, and most importantly, used a different ribavirin dose regimen to APRICOT. Of the 37 pegIFNα-2a (40KD) plus ribavirin recipients in the ACTG A5071 trial who had not achieved a virological response at week 24, 26 underwent liver biopsy. The histological response rate in the 26 patients was 35%, which is identical to the histological response rate in virological non-responders in APRICOT (12 of 34; 35%). In contrast, no significant improvement in necroinflammatory grade or fibrosis stage occurred in virological non-responders to pegIFNα-2b (12KD) plus ribavirin or conventional IFNα-2a plus ribavirin in a multicenter French study (overall histological response rates were not reported in that trial) [11].

Overall, the favorable histological responses seen with interferon-based therapies suggest that, in addition to having antiviral and immunomodulatory effects, interferon-based therapies also have antiproliferative effects. The exact mechanism by which IFNα reverses the progression of hepatic fibrosis is not known, but may well be mediated by direct or indirect effects on hepatic stellate cells [12–14]. Histological response may therefore be considered to be an alternative treatment goal in patients who do not achieve an early virological response at week 12. For this reason, maintenance therapy against HCV with pegIFNα-2a (40KD) is being investigated in the HALT-C, EPIC and COPILOT trials in HIV-negative patients and in HIV-positive patients enrolled in the SLAM-C study.

In conclusion, the histological response rate in APRICOT was significantly higher in patients with HIV–HCV co-infection who received pegIFNα-2a (40KD) plus ribavirin than in those receiving pegIFNα-2a (40KD) plus placebo or IFNα-2a plus ribavirin. Histological response was correlated with virological response, although it should be noted that a substantial proportion of patients who did not achieve an SVR experienced histological improvement.

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