

Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients

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Background: Current therapies for chronic hepatitis C virus (HCV) in HIV co-infected patients have a low success rate and are poorly tolerated. We have evaluated the efficacy and safety of interferon alfa-2b (IFN) + ribavirin (RBV) versus pegylated interferon alfa-2b (PEG-IFN) + RBV.

Methods: Randomized, single-centre, open-label clinical trial including patients with: detectable HCV-RNA, alanine aminotransferase > 1.5-fold upper limit of normal, abnormal liver histology, CD4 cell count > 250 × 10⁶/l and HIV RNA < 10 000 copies/ml. Patients were assigned to INF (3 × 10⁶ units three times/week) or PEG-IFN (100–150 µg/week) plus RBV (800–1200 mg/day). Duration of treatment was 48 weeks (only 24 weeks for HCV genotypes 2 or 3 and baseline HCV RNA < 800 000 IU/ml). The primary endpoint was a sustained virological response (SVR).

Results: Ninety-five patients were randomized (43 INF + RBV, 52 PEG-IFN + RBV), 68% males, 82% injecting drug users; 63% genotypes 1 or 4 and 36% genotypes 2 or 3; 62% fibrosis index grade ≥2 and 30% bridging fibrosis/cirrhosis. SVR was significantly higher in the PEG-IFN + RBV arm, 44% versus 21% (intent to treat; *P* = 0.017). Among patients with genotypes 1 or 4, SVR were 38% versus 7% (*P* = 0.007) and 53% versus 47% (*P* = 0.730) for genotypes 2 or 3. CD4 cell count but not its percentage dropped in both arms and HIV RNA viral load did not change from baseline. Side effects were very frequent in both arms leading to treatment discontinuation in 14 patients without statistical differences between arms (*P* = 0.565).

Conclusion: PEG-IFN + RBV was significantly more effective than INF + RBV for the treatment of chronic hepatitis C in HIV co-infected patients, mainly of genotype 1 or 4.

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Introduction

Liver disease caused by chronic hepatitis C virus (HCV) infection is now a leading cause of morbidity and mortality among HIV-infected patients in the developed world, where classic opportunistic complications of severe immunodeficiency have declined dramatically as a result of the widespread use of highly active antiretroviral therapy [1,2]. Given that HIV and HCV share a similar route of transmission, the overall prevalence of chronic hepatitis C in patients with HIV is about 33% [3], ranging from 75% to 90% when a prior medical history of injecting drug use is reported [4].

In this setting, co-infection with HCV has become a leading cause of death and hospital admission in HIV infected patients [5]. Chronic hepatitis C has been shown to exhibit an accelerated progression to liver fibrosis in HIV infected patients as compared with HIV-seronegative immunocompetent individuals [6]. HCV co-infection may limit the adequate treatment of HIV and is associated with an increased toxicity of antiretroviral drugs [7]. Thus, the adequate management of HCV-related chronic liver disease in HIV infected patients is a major concern in this population.

Combined treatment with interferon plus ribavirin (RBV) has been the gold standard for HCV treatment since 1998 [8,9]. However, there are few data on combined therapy for HCV in HIV co-infected patients. Most published studies are observational and yield low rates of sustained virological response ranging from 20% [10,11] to 40% [12]. A new formulation of interferon has been developed and now pegylated interferon plus RBV may become the cornerstone of therapy for chronic hepatitis C [13,14]. To date, however, there is little published information about the safety and efficacy of combined treatment with pegy-

lated interferon plus RBV in HIV co-infected patients. Preliminary results of clinical trials and some observational studies have shown a lower efficacy of the combination in this population and a higher rate of adverse events [15–18]. Recently, three randomized studies were presented with an overall sustained virological response (SVR) rate for the pegylated interferon + RBV arms ranging from 26% up to 40% [19–21].

The objective of our study was to assess the efficacy and safety, in terms of SVR and adverse events, of interferon alfa-2b (IFN) + RBV versus pegylated interferon alfa-2b (PEG-IFN) + RBV in previously untreated HCV patients co-infected with HIV.

Methods

Patients

Patients were selected among HIV–HCV co-infected patients who received medical care for their HIV infection between April 2001 and October 2002. The patients had to fulfil the following inclusion criteria: previously untreated chronic hepatitis C with HCV RNA positive in plasma, alanine aminotransferase (ALT) > 1.5-fold the upper limit of normal and histological modifications in the liver biopsy (fibrosis > 1 or/and necroinflammatory activity); control of HIV infection with a viral load < 10 000 copies/ml and a CD4 cell count > 250 × 10⁶ cells/l, in response to a stable antiretroviral treatment (ART) or without ART if it was not required. Exclusion criteria were the presence of other causes of hepatopathy, decompensated cirrhosis, pregnancy and potential contraindications for interferon or for ribavirin therapy such as haemoglobinopathies, cardiopathy, autoimmune diseases, major depression or other severe psychiatric pathologies and active illicit drug consumption within the last 12 months.

Study design and organization

The study was a prospective, single-centre, randomized open-label trial carried at the specialized HIV unit of the Hospital Clinic, a tertiary centre in Barcelona, Spain at which more than 2500 HIV patients are receiving care. The centre's institutional ethics committee approved the protocol and all patients provided written informed consent before entering in the study.

Treatment and monitoring

Eligible patients were randomly assigned to one of the two study treatments in equal proportions (Fig. 1) by means of a computer generated table of random numbers. The first treatment group, arm A, received PEG-IFN (Peg-Intron A; Schering Corporation, Kenilworth, NJ, USA), subcutaneously at a dose of 100 µg when body weight was < 75 kg or 150 µg when it was

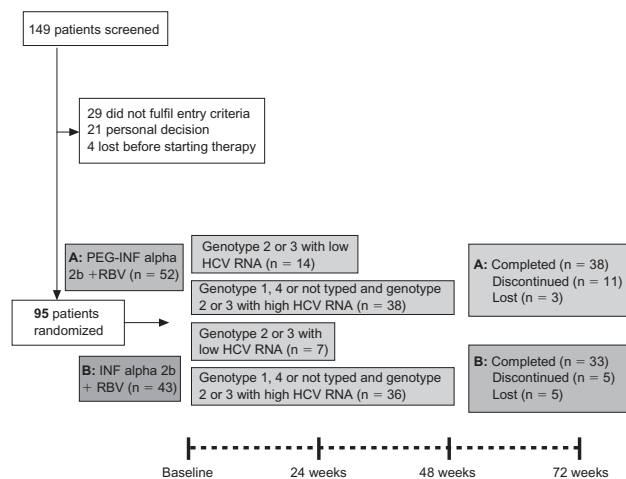


Fig. 1. Trial profile.

75 kg or more, each week plus oral RBV (Rebetol; Schering Corporation) every day. The second group, arm B, received IFN (Intron A; Schering Corporation), 3×10^6 units subcutaneously three times/week plus daily oral RBV. The dose of RBV was adjusted to body weight: 800 mg when the body weight was < 60 kg, 1000 mg when it was between 60 and 75 kg, and 1200 mg when body weight was > 75 kg. RBV was administered in two divided doses per day. The duration of the therapy was 48 weeks for all patients with the exception of those with HCV genotypes 2 or 3 and HCV RNA at baseline below 800 000 IU/ml who received only 24 weeks of therapy.

Patients were evaluated before beginning treatment, 2 weeks after starting therapy and every 4 weeks until the cessation of therapy, and also at 12 and 24 weeks after cessation of therapy to evaluate the SVR. A blood analysis including a haemogram and a complete biochemistry with lactate was carried out at every medical visit, in addition to a medical interview to establish possible secondary effects of the treatment. At week 4 and every 12 weeks thereafter we also determined the thyroid function; the HIV viral load and the CD4 T cell count. Serum HCV RNA was measured by a quantitative PCR assay at baseline, before starting treatment, and 12 weeks after starting therapy (Cobas AmpliPrep/Cobas Amplicor HCV Monitor Test version 2.0; sensitivity 500 copies/ml; Roche Molecular Systems Inc., Branchburg, New Jersey, USA). During treatment at weeks 4, 24, 36 and 48 and at 12 and 24 weeks after cessation of therapy HCV RNA was measured by a qualitative PCR assay (Cobas AmpliPrep/Cobas Amplicor HCV test version 2.0; sensitivity of 50 copies/ml; Roche Molecular Systems). Genotyping was carried out as described previously [22]. Liver biopsy was performed in all patients before randomization. All biopsy samples were analysed by a single pathologist in our hospital and graded according to Scheure's classification [23].

Assessment of efficacy

The primary measure of efficacy was the SVR, defined as undetectable HCV RNA in serum at the end of follow up (24 weeks after cessation the treatment) by an intent-to-treat (ITT) analysis. Patients with detectable HCV RNA after 24 weeks of therapy were considered failures and therapy was discontinued. Secondary parameters of efficacy were: the rate of virological response (VR) at the end of treatment, the rate of sustained biochemical response (SBR) defined as the presence of normal ALT values at the end of 24 weeks of follow up and the rate of relapses defined as patients with VR but not SVR.

Assessment of safety

Adverse events were graded as mild, moderate, severe, or potentially life-threatening according a modification

of the World Health Organization scale [24]. Therapy was permanently discontinued for life-threatening events. For severe adverse events other than anaemia, the dose of IFN, PEG-IFN or RBV could be decreased by 50%. Full doses could be restarted when the event abated. For anaemia, the RBV dose was lowered to 50% for falls in haemoglobin of < 100g/l, and RBV was discontinued if haemoglobin concentrations fell to < 85g/l. Full doses of RBV could be restarted when the haemoglobin increased to the normal level for that patient. The interferon dose could be halved if the polymorph nuclear lymphocyte count decreased to < 750×10^6 cells/l or the platelet count decreased to < 60×10^6 cells/l. Treatment was discontinued when the lymphocyte count fell to < 500×10^6 cells/l or platelets fell to < 50 000 cells/ml. Neither granulocyte colony stimulating factor nor erythropoietin was used in this study.

Statistical analysis

A descriptive analysis of the baseline variables was conducted looking at the central tendency and dispersion. These values were compared with the aim of ensuring that the demographic, epidemiological, clinical, biochemical and histopathological characteristics were similar among the patients in the two therapy groups.

The inferential analysis of the continuous quantitative variables were performed, when possible, by means of parametric tests (Student's t test). The analysis of the dichotomic variables (response/no response) was made by means of contingency tables (Chi-squared test or Fisher's exact test). Analyses were done by ITT on the whole treated population (all patients who received at least one dose of study medication) and by 'on treatment' (OT). In addition, a logistic regression analysis was carried out using the SVR as the dependent variable. Univariate logistic regression was used to confirm the importance of previously identified prognostic factors. To assess the independence of these factors, a backward elimination procedure was then undertaken using the factors that were significant in the univariate analyses. All reported *P* values are two-sided. The data were analysed in the Epidemiology and Statistics Unit, UASP, Hospital Clinic, Barcelona, Spain.

The sample size (90 patients; 45 in each treatment arm) was calculated on the basis of a bilateral test of comparison of a proportion observed with respect to a theoretical proportion [25]. We assumed a response rate of 60% in the group with PEG-INF therapy and wanted to detect differences ≥ 20 percentage points if they exist in the INF group therapy; with an alpha risk of 0.05 and a power of 80%.

Results

Patients' characteristics

Enrolment began in April 2001, and the trial was completed in February 2004. A total of 149 patients were screened; 95 were included, received at least one dose of medication and were evaluated in the ITT analyses, both by efficacy and safety (see Fig. 1). Baseline characteristics including histological findings in liver biopsies were similar between the two groups (Table 1). The majority of the patients were male (68%) with a mean age of 40 years. Eighty two per cent of the subjects had a history of illicit injecting drug use. The mean time of known chronic HCV infection was 17 years. The more frequent HCV genotypes in our series were 1 and 3 (49% and 33%, respectively). Sixty-two per cent of the study participants had a fibrosis index of grade 2 or above, and one-third had a bridging fibrosis or cirrhosis in the liver biopsy.

Eighty-four patients (88%) were receiving ART during the study period. Most of them a regimen containing two nucleoside analogue reverse transcriptase inhibitors plus one non-nucleoside analogue reverse transcriptase inhibitor. The mean duration of previous treatment for HIV infection was 63 months. Sixty-seven patients (70%) had a baseline HIV RNA plasma levels < 200 copies/ml. The mean CD4 T cell count before starting the HCV therapy was 560×10^6 cells/l.

Outcome

Response rates are summarized in Table 2 and Fig. 2. In the global analyses by ITT, 34% of patients reached SVR. This rate was significantly higher for the group receiving PEG-INF than for the INF treatment group,

44% versus 21% ($P = 0.017$). By OT analyses the response rates were 59% PEG-INF and 27% INF ($P = 0.007$). In genotypes 1 or 4 the difference of SVR by ITT analyses between groups of treatment was 38% in the PEG-INF arm versus 7% in the INF arm ($P = 0.007$); by OT analyses it was 52% versus 10% ($P = 0.002$). In genotypes 2 or 3 the rates of SVR for the two groups were similar: 53% versus 47% ($P = 0.730$) by ITT analyses and 67% versus 64% ($P = 0.873$) by OT analyses.

Patients with baseline low levels HCV RNA (< 800 000 IU/ml) reached better rate of SVR than patients with basal HCV RNA $\geq 800 000$ IU/ml: 49% versus 22% ($P = 0.007$). The response rate was different depending on the degree of fibrosis in the liver; for fibrosis grades 0–2, VR was 48% versus 29% in the group with most advanced fibrosis (grades 3–4). However the SVR was similar, 36% versus 29% ($P = 0.467$), due to a higher number of relapses in the group with a lower degree of fibrosis. The overall SBR rate was 45%. Although the patients assigned PEG-INF had better results, the difference did not reach statistical significance: 53% versus 33% ($P = 0.079$). Among patients with SVR, six (20%) did not achieve normal values of ALT at the end of follow up. The proportion of patients who cleared virus but who relapsed by the end of follow-up was small in both treatment groups (8% PEG-INF arm, 9% INF arm). It is important to note that the three patients who relapsed were HCV genotypes 2 or 3 with a baseline HCV RNA < 80 000 copies/ml and assigned to a 6-month regimen.

To examine the influence of potentially important prognostic factors on SVR we assessed by univariate

Table 1. Baseline characteristics of the patients. None of the differences were statistically significant (Chi-squared test).

	PEG + RBV (n = 52)	INF + RBV (n = 43)	Total (n = 95)
Mean age (years)	40	40	40
Sex, male (%)	63	74	68
Mean body weight (kg)	62	64	63
HIV-1 risk factor (% injecting drug users)	75	91	82
Mean duration of HIV infection (years)	10	12	11
Patients on antiretroviral therapy (%)	94	81	88
Mean baseline CD4 cell count ($\times 10^6$ cells/l)	570	556	560
Baseline HIV viral load (copies/ml)	199	199	199
Hepatitis C virus genotype (%)			
1	55	43	49
2	4	2	3
3	33	33	33
4	8	21	14
Not typable	0	2	1
HCV RNA (% < 800 000 IU/ml)	53	38	46
Mean duration of HCV infection (years)	17	17.5	17
Mean inflammatory Scheure's score	3	4	3
Scheure's fibrosis score (%)			
0–2	71	69	70
3–4	29	31	30

RBV, Ribavirin; PEG, pegylated interferon alfa-2b; INF, interferon alfa-2b.

Table 2. Percentages of virological response (VR) and 24-week sustained virological response (SVR) by intent-to-treat analysis.

	PEG + RBV (n = 52)	INF + RBV (n = 43)	Total (n = 95)	<i>P</i>
Overall (n = 95)				
VR	52	30	42	0.033 ^a
SVR	44	21	34	0.017 ^a
SVR by genotype				
1 or 4 (n = 59)	38	7	24	0.007 ^a
2 or 3 (n = 34)	53	47	50	0.730 ^a
SVR by degree of fibrosis				
0–2 (n = 66)	49	21	36	0.019 ^a
3–4 (n = 28)	33	23	29	0.549 ^a
SVR by baseline HCV RNA				
< 800 000 IU/ml (n = 43)	60	31	49	0.076 ^b
≥ 800 000 IU/ml (n = 50)	30	15	22	0.240 ^b
SVR by dose of therapy				
No modification (n = 57)	37	11	25	0.033 ^b
Dose reduction (n = 38)	55	38	47	0.342 ^b

^aChi-squared test. ^bFisher's exact test, RBV, Ribavirin; PEG, pegylated interferon alpha-2b; INF, interferon alpha-2b; HCV, hepatitis C virus.

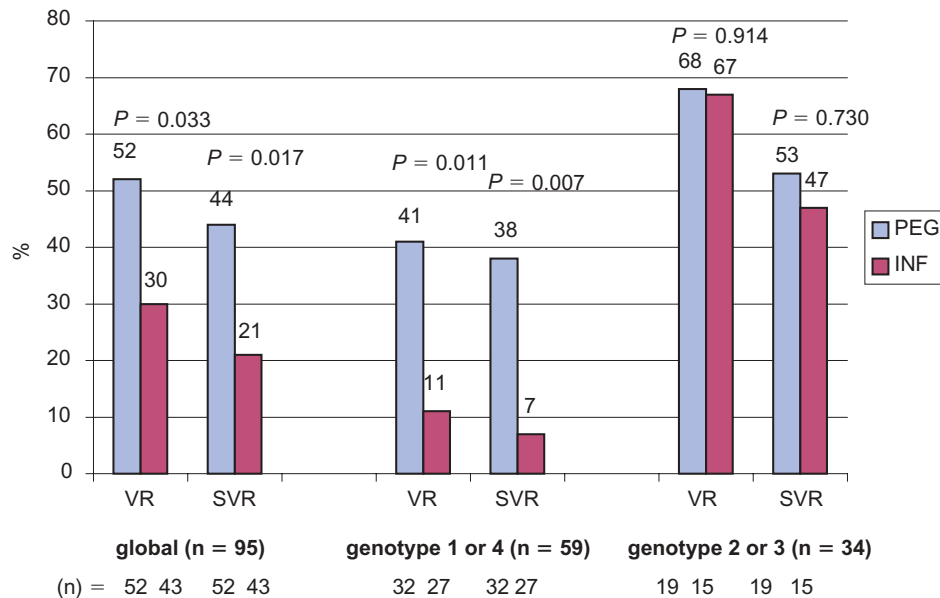


Fig. 2. Response rate by intent-to-treat analysis. VR, Virological response at end of therapy; SVR, sustained virological response 24 weeks after cessation of therapy.

and multivariate methods the following variables: HCV genotype, baseline HCV RNA, degree of fibrosis in the liver sample before start of therapy, years with HCV infection, baseline CD4 cell count, baseline HIV VL, Centers for Disease Control classification at baseline, years with HIV infection, ART or no therapy for HIV, risk group, age, sex, baseline body weight, kind of interferon drug and the necessity or not to modify the dose of HCV therapy (Table 3). HCV genotypes 2 or 3 ($P = 0.011$), baseline HCV RNA < 800 000 IU/ml ($P = 0.008$) and PEG-INF therapy ($P = 0.019$) were significantly associated with a better SVR. Female sex and modifications in the dose of study medication

due to side effects almost reached significance and were also included in the multivariate analysis. Only genotype 2 or 3 ($P = 0.006$), PEG-INF based therapy ($P = 0.025$) and the dose modification of assigned drugs remained as independent predictors associated with a better SVR.

Safety evaluation

The side-effect profiles of PEG-INF + RBV and INF + RBV were similar; there were no unexpected or unique adverse events (Table 4). There was a substantial increase in injection site reactions in the PEG-INF group compared with the INF group but the difference

Table 3. Univariate and multivariate analysis of outcome (sustained virological response) predictors. For multivariate analysis only statistically significant values were included in the table.

Variable	Crude odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)	P
Age (years)				
≥ 40	1	0.949		
< 40	0.9 (0.4–2.3)			
Sex				
Male	1	0.072		
Female	2.3 (0.9–5.6)			
Body weight (kg)				
> 60	1	0.229		
≤ 60	1.7 (0.7–4.4)			
Years with HCV	0.9 (0.8–1.1)	0.159		
Risk factor				
Others	1	0.472		
Injecting drug use	0.7 (0.2–1.9)			
Years with HIV	1 (0.9–1.1)	0.971		
Alcohol (> 20 mg/day)				
No	4.4 (0.7–26)	0.255		
Yes	0.9 (0.2–4)			
CDC classification				
A	1	0.316		
B	0.6 (0.1–3.6)			
C	0.4 (0.1–1.3)			
Antiretroviral therapy				
Yes	1	0.634		
No	0.7 (0.1–2.9)			
≥ 350	1	0.695		
< 350	0.8 (0.3–2.3)			
HIV viral load (copies/ml)				
≥ 200	1	0.496		
< 200	1.4 (0.5–3.6)			
HCV genotype				
1–4	1	0.011	1	0.006
2–3	3.2 (1.3–7.9)		4.1 (1.5–11.2)	
Fibrosis score				
0–2	1	0.467		
3–4	0.7 (0.2–1.8)			
HCV RNA (IU/ml)				
≥ 800 000	1	0.008		
< 800 000	3.4 (1.3–8.3)			
Therapy modification				
No	1	0.074	1	0.036
Yes	2.8 (1.1–7.4)		3.2 (1.1–8.6)	
Kind of interferon				
PEG	1	0.019	1	0.025
INF	0.3 (0.1–0.8)		0.3 (0.1–0.85)	

CI, Confidence interval; CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus. ($\times 10^6$ cells/l)

was not statically significant. The typical event was generally mild, not treatment limiting, and characterized by localized erythema. Influenza-like syndrome was the most frequent adverse effect related to therapy: it appeared in more than 80% of patients at the beginning of treatment and improved within a few weeks.

Anaemia was the most frequent haematological adverse event (Fig. 3) with an overall prevalence of (27%), 31% for the PEG-INF + RBV regimen compared with 23% for the INF + RBV regimen, being mild or moderate in most cases. A decrease in haemoglobin to < 100 g/l,

the protocol requirement for dose modification, occurred in 13% of patients and discontinuation for anaemia was rare (one patient). Neutropenia was present in 22% of patients (27% for the PEG-INF arm compared with 16% for INF arm). The frequency of dose reduction for neutropenia according to the protocol was 9%; however, no patients discontinued treatment for this reason. A thrombocytopenia appeared in 20% of patients (25% PEG-INF compared with 14% for INF regimen); 3% of patients had a platelet decrease that reached the protocol-defined criterion for dose reduction and one patient discontinued therapy due to thrombocytopenia.

Table 4. Percentages of discontinuation of treatment, dose reduction and overall adverse events of any grade during treatment.

	PEG + RBV (n = 52)	INF + RBV (n = 43)	Total (n = 95)	<i>P</i> ^a
Discontinuation				
Any reason	23	14	19	0.245
Adverse effect	17	12	15	0.565
Dose reduction for:				
Any adverse event	42	37	40	0.677
Anaemia	12	16	14	0.559
Neutropenia	13	7	11	0.504
Thrombocytopenia	6	5	5	1
General symptoms				
Influenza-like	88	74	82	0.107
Asthenia	69	81	75	0.237
Anorexia	48	30	40	0.094
Headache	23	23	23	1
Myalgia	37	23	31	0.185
Haematological findings				
Anaemia	31	23	27	0.491
Neutropenia	27	16	22	0.321
Thrombocytopenia	25	14	20	0.207
Gastrointestinal symptoms	17	19	18	1
Psychiatric symptoms				
Depression	37	51	43	0.212
Irritability	27	42	34	0.135
Insomnia	21	19	20	0.802
Dermatological symptoms				
Alopecia	25	16	21	0.325
Injection site reaction	21	7	15	0.080
Mitochondrial toxicity	2	7	4	0.325
Thyroid dysfunction	12	5	8	0.286

^aFisher's exact test. RBV, Ribavirin; PEG, pegylated interferon alfa-2b; INF, interferon alfa-2b.

Forty-one (43%) patients developed symptoms of depression (sadness, tiredness, apathy) during the therapy (37% for PEG-INF versus 51% for INF). Fifteen of them (37%) were treated with citalopram, a selective serotonin re-uptake inhibitor, resulting in a significant improvement in their symptoms. Two patients interrupted the interferon-based therapy due to severe psychiatric pathology: one psychotic episode in a patient with no previous history of psychiatric events and one major depression.

During the treatment period, eight patients developed biochemical thyroid dysfunction, and four of these patients presented secondary symptoms: three cases of hypothyroidism that needed substitution therapy with levothyroxin, and one case of hyperthyroidism treated with metimazol. None of them had to stop the HCV therapy for this reason.

Biochemical mitochondrial toxicity defined as hyperlactatemia (lactate > 20 mg/dl) and/or increase in pancreatic enzymes (amylase/lipase > 400/200 IU/l) was present in nine patients during the study period. Only one case had symptomatic mitochondrial toxicity: weight loss, abdominal pain, nausea and vomiting. This patient discontinued ART (stavudine, lamivudine and

saquinavir) and HCV therapy leading to complete recovery.

There were no cases of descompensated liver disease in our series.

Fourteen (15%) out of 95 patients included in the study discontinued treatment due to adverse events, nine in the PEG-INF arm and five in the INF arm. The major causes were: a severe influenza-like syndrome (eight cases); lactic acidosis (one case); psychiatric pathology (two cases); severe anaemia requiring blood transfusion (one case); thrombocytopenia (one case); and after a heart stroke (one case). Two patients decided to withdraw therapy before 24 weeks, and two additional patients stopped the therapy due to a protocol violation (use of injecting drugs).

At baseline, the mean CD4 cell count was 560×10^6 cells/l. In the follow up there was a decrease to a mean of 331×10^6 cells/l, but the percentage of CD4 cells remained stable (Fig. 3). In 19 patients the CD4 cell count decreased to $< 200 \times 10^6$ cells/l but we did not observe any opportunistic infection. Regarding HIV viral load, we did not observe meaningful changes during follow up.

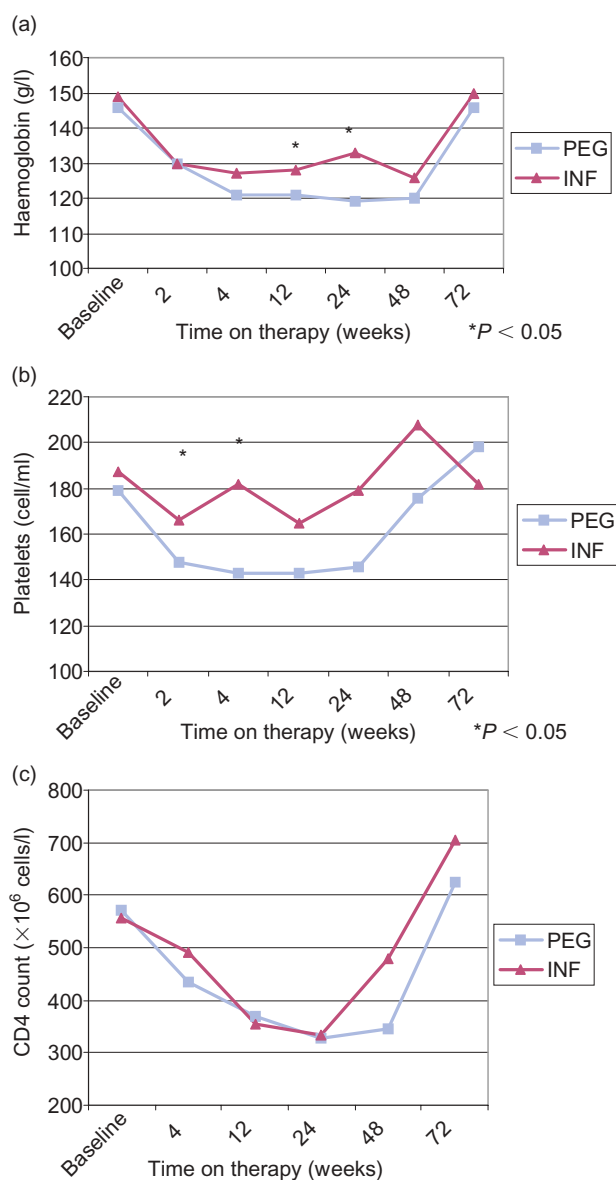


Fig. 3. Evolution of haematological parameters during therapy. (a) Mean haemoglobin. (b) Mean platelet count. (c) mean CD4 cell count.

Discussion

In our study PEG-IFN + RBV was significantly more effective than IFN + RBV for the treatment of chronic hepatitis C in HIV co-infected patients. In concordance with published data in the literature from open non-randomized studies [17,18], the rate of SVR was lower than that reported with PEG-INF + RBV in mono-infected HCV patients [13,14]. However, the rate of global SVR achieved in our study was better than the rate described in previous trials and similar to the recently communicated final results of APRICOT study [19]. The benefit of the PEG-INF versus INF regimen was most apparent for patients with genotype

1, the subgroup that is most common and the most difficult to treat.

In our series, genotypes 2 or 3, PEG-INF therapy and dose modification of assigned drugs were independent factors associated with a better SVR. Of note is the fact that a dose reduction was not associated with worst outcome. Conversely this group had a better SVR, possibly related to a smaller rate of withdrawals. Although some authors have related the basal HCV RNA values with the rate of SVR [14,17] this variable was not selected as an independent factor for SVR probably due to the relatively small number of patients and the fact that three patients with a low baseline HCV RNA levels and genotypes 2 or 3 relapsed after 6 months of therapy. Also, some studies found a relationship between the degree of fibrosis and the rate of SVR [13,14]. We observed a tendency to achieve a lower rate of response in patients with higher degree of fibrosis but, in our study, we did not find any statistically significant difference.

In studies in HCV mono-infected patients, most of those who reached a SVR also had normal ALT levels at the end of follow up [13,14]. In our series, however, 20% of patients with SVR remained with ALT values over the upper limit of the normal range. This could be due to a toxic effect on the liver of some antiretroviral drugs. For this reason, the biochemical response in HCV-HIV co-infected patients is not a good marker of virological response.

Side effects secondary to HCV therapy were very frequent (> 90%), but in the majority of cases were mild or moderate. It seems that some of these side effects (influenza-like syndrome, local reactions in the skin or anorexia) were most prevalent in the patients treated with PEG-INF, but we did not find statistically significant differences between the two therapy groups. Abnormal haematological parameters were present in one-fifth of patients but only half of them needed modifications in drug dosage. Total CD4 cell count decreased in both arms but no evidence of deleterious effect on HIV control were seen.

Of special concern are two important types of side effects. The first one is the high incidence of depressive symptoms in co-infected patients treated with interferon-based therapy. Most of them were not severe and improved with antidepressant therapy, without reduction or cessation of HCV therapy. We recommended close assessment of psychiatric symptoms during the first weeks after initiating interferon-based therapy in HIV-HCV co-infected patients. Early treatment of these side effects with antidepressants would help to avoid early dropouts from therapy [26]. The second type is a side effect not previously reported in mono-infected patients on HCV therapy, but well described

in co-infected patients on ART who begin HCV therapy: mitochondrial toxicity [27]. This side effect is related to the fact that RBV, a nucleoside analogue, is able to inhibit the mitochondrial gamma polymerase and to interfere in the intracellular metabolism of didanosine [28]. In our series mitochondrial toxicity occurred in 12% of patients; although most cases were asymptomatic, concomitant use of ribavirin plus ART containing nucleoside analogues such as didanosine or stavudine, should be cautioned against or not recommended [29].

Is well known that HIV–HCV co-infected patients have higher rates of therapy withdrawal than mono-infected patients. This may simply reflect a higher rate of serious adverse events in this population compared with HIV-negative individuals. In the present study, the rate of premature discontinuation due to adverse effects was 15%; this rate is lower than previous reports in co-infected HIV–HCV patients [10,18,21]. A potential explanation is that all patients were recruited in a single centre and were managed by the same multidisciplinary and experienced team.

In summary, PEG-IFN + RBV provides a considerable clinical advantage over therapy with IFN + RBV in HIV–HCV co-infected patients, and the difference was driven mainly by the better results among patients with HCV genotypes 1 or 4.

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