Tratamiento e historia natural de la hepatitis crónica C en pacientes coinfectados por VIH-1

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Tesis Doctoral

TRATAMIENTO E HISTORIA NATURAL DE LA HEPATITIS CRÓNICA C EN PACIENTES COINFECTADOS POR VIH-1

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ANEXO 1:PUBLICACIONES

Randomized Trial Comparing Pegylated Interferon α-2b Versus Pegylated Interferon α-2a, Both Plus Ribavirin, to Treat Chronic Hepatitis C in Human Immunodeficiency Virus Patients

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Although two pegylated interferons (Peg-IFN) are available to treat chronic hepatitis C virus (HCV) infection, no head-to-head comparative studies have been published. We aim to compare the efficacy and safety of PEG IFN alfa-2b (PEG 2b) versus PEG IFN alfa-2a (PEG 2a), plus ribavirin (RBV). A prospective, randomized, multi-center, open-label clinical trial including 182 human immunodeficiency virus (HIV)–hepatitis C virus (HCV) patients naïve for HCV therapy was performed. Patients were assigned to PEG 2b (80-150 μg/week; n = 96) or PEG 2a (180 μg/week; n = 86), plus RBV (800-1200 mg/day) for 48 weeks. The primary endpoint was sustained virological response (SVR: negative HCV-RNA 24 weeks after completion of treatment). At baseline, both groups were well balanced: 73% male; 63% HCV genotype 1 through 4; 29% had fibrosis index of 3 or greater. The overall SVR was 44% (42% PEG 2b versus 46% PEG 2a, $P = 0.65$). Among genotypes 1 through 4, SVRs were 28% versus 32% ($P = 0.67$) and 62% versus 71% ($P = 0.6$) in genotypes 2 through 3 for PEG 2b and PEG 2a, respectively. Early virological response (EVR; ≥2 log reduction from baseline or negative HCV-RNA at week 12) was 70% in the PEG 2b group and 80% in the PEG 2a group ($P = 0.13$), reaching a positive predictive value of SVR of 64% and a negative predictive value of 100% in both arms. Side effects were present in 96% of patients but led to treatment discontinuation in 10% of patients (8% on PEG 2b and 13% on PEG 2a, $P = 0.47$). *Conclusion:* In patients with HIV, HCV therapy with PEG 2b or PEG 2a plus RBV had no significant differences in efficacy and safety. (HEPATOLOGY 2009;49:22-310.)

Liver disease caused by chronic hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality among human immunodeficiency virus (HIV)-infected patients in the developed world and represents an important health care problem in this population[1,2]; thus, the adequate management of HCV-related chronic liver disease in HIV-infected patients arises as a major priority.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral treatment; EVR, early virological response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NPV, negative predictive value; PEG IFN, pegylated interferon; PEG 2a, pegylated interferon alfa 2a; PEG 2b, pegylated interferon alfa 2b; PPV, positive predictive value; RBV, ribavirin; RVR, rapid virological response; SVR, sustained virological response.

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Over the past years, we have experienced a great advance in the knowledge of the natural history of this chronic infection and the possible interactions between both viruses in co-infected individuals,[3-6] and we have explored the efficacy of different drugs for viral eradication. Pegylated interferon (PEG IFN) combined with ribavirin (RBV) has become the gold standard for HCV treatment in HIV co-infected patients since 2004.[7-10]

Two formulations of PEG IFN alpha are currently available on the market: PEG IFN alfa-2a (PEG 2a) and PEG IFN alfa-2b (PEG 2b) with similar patterns of adverse effects.[11,12] The efficacy data, measured by the sustained virological response (SVR), range between 22% and 55% depending on the study that we analyzed.[7-10,13-15] These two drugs differ in terms of their chemical structure and pharmacokinetic properties[11,12]; these differences, as well as the study design and patient population included in each trial, may account for the variation in the rate of SVR across studies. Despite the existence of consistent data on the therapeutic efficacy of both molecules in co-infected patients,[7-10,13-15] no head-to-head comparisons between the two pegylated interferons have been published so far. In HCV-monoinfected patients[16-19] and recently in HIV co-infected patients,[20] cross-study comparisons and retrospective analyses of previous data have been published; however, these results are difficult to interpret because trials were not randomized, and the study design, doses of anti-HCV drugs, and baseline characteristics of patients were not consistent among studies. Only preliminary data from two different prospective, comparative studies on HCV-monoinfected patients have been reported recently.[21,22] Therefore, we aimed to prospectively compare the efficacy and safety, in terms of SVR and adverse events, of PEG 2b plus RBV versus PEG 2a plus RBV in previously untreated HCV patients co-infected with HIV.

Patients and Methods

Patients. HIV-HCV co-infected individuals who received medical care for HIV infection were consecutively enrolled between January 2003 and March 2006. The patients had to fulfill the following inclusion criteria: previously untreated chronic hepatitis C with positive HCV-RNA in plasma, alanine aminotransferase (ALT) levels greater than 1.5-fold higher than the upper limit of normal, and histological modifications in the liver biopsy; control of HIV infection with CD4+ cell count above 250 cells/mm^3, and HIV viral load lower than 50.000 copies/mL, in response to a stable antiretroviral treatment (ART) or without ART if not required. Exclusion criteria were presence of other causes of hepatopathy, decompensated cirrhosis, pregnancy, and formally known contraindications for PEG IFN or RBV therapy such as hemoglobinopathies, cardiopathy, autoimmune diseases, major depression or other severe psychiatric pathological conditions, and active illicit drug consumption within the last 12 months.

Study Design and Participating Centers. The study was a prospective, multicenter, randomized, open-label trial carried out in the specialized HIV units of five hospitals of Spain (Hospital Clinic, Barcelona; Hospital Son Llàtzer, Palma de Mallorca; Hospital Son Dureta, Palma de Mallorca; Hospital Joan XXIII, Tarragona; Hospital Germans Trias i Pujol, Badalona). The institutional ethics committee approved the protocol in each center, and all patients provided written informed consent before entering the study.

Treatment and Monitoring. Eligible patients were randomly assigned to one of the two study treatments in equal proportions by means of a computer-generated table of random numbers. The first treatment group received PEG 2b (Peg-Intron, Schering Corp., Kenilworth, NJ) subcutaneously (80-150 μg adjusted to body weight) once per week, plus daily oral RBV (Rebetol, Schering Corp.). The second group received PEG 2a (Pegasys, F. Hoffmann-La Roche Ltd., Basel, Switzerland) subcutaneously (180 μg) once per week, plus daily oral RBV (Copegus, F. Hoffmann-La Roche). The dose of RBV was adjusted to body weight: 800 mg for body weight below 60 kg, 1000 mg when it was between 60 and 75 kg, and 1200 mg when it was above 75 kg. The dose of RBV was divided into two daily doses. The duration of therapy was 48 weeks for all patients.

Patients were evaluated before treatment, 2 weeks after initiation of treatment, and every 4 weeks thereafter until cessation of therapy. One last evaluation was performed 24 weeks after cessation of therapy to evaluate the SVR. A complete cell count and routine chemistry tests including lactate were conducted at every medical visit, as well as a medical interview to monitor possible secondary effects associated with treatment. Thyroid function, plasma HIV viral load, and CD4+ cell count were also evaluated at week 4 and every 12 weeks thereafter. Serum HCV-RNA was measured by a quantitative polymerase chain reaction assay at baseline, and 12 weeks after initiation of therapy [Versant HCV-RNA 3.0 (bDNA), Siemens Medical Solutions Diagnostics, Tarrytown, NY]. HCV-RNA was measured by a qualitative polymerase chain reaction assay (Versant HCV RNA Qualitative Assay, Siemens Medical Solutions Diagnostics) with a sensitivity of 30 IU/mL during weeks 4, 24, 36, and 48 of treatment, and 24 weeks after cessation of treatment. HCV genotyping was done as previously described.[23] Liver biopsy was performed in all

patients before randomization, and biopsy samples were analyzed and graded according to Scheuer's classification.[24]

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 of 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 early virological response (EVR), defined as negative HCV-RNA or a 2 or greater log reduction of HCV-RNA from baseline at week 12 of treatment; the rate of rapid virological response (RVR), defined as negative HCV-RNA at week 4 of treatment; sustained biochemical response, defined as the presence of normal ALT values at the end of 24 weeks of follow-up; and the rate of relapse, defined as patients with end-of-treatment response but not SVR. Finally, we analyzed the positive predictive value (PPV) and negative predictive value (NPV) to achieve the SVR for those patients with RVR and EVR.

Assessment of Safety. Adverse events were graded as mild, moderate, severe, or potentially life-threatening according to a modification of the World Health Organization scale.[25] Therapy was permanently discontinued in patients developing life-threatening events. In cases of hematological toxicity, the RBV or PEG IFN dose was lowered according to the drug label recommendations,[11,12] and full doses were restarted when the hematological parameters returned to previously normal levels for that patient. The use of granulocyte colony-stimulating factor and erythropoietin was permitted in this study and used at the discretion of the doctor responsible for each patient.

Statistical Analysis. A descriptive analysis of the baseline variables was conducted, including measures of central tendency and dispersion. These values were compared to ensure that the demographic, epidemiological, clinical, laboratory, and histopathological characteristics were similar between both groups of therapy. The inferential analysis of the continuous quantitative variables was performed, when possible, by means of a parametric test (Student *t* test) or a nonparametric test (*U*—Mann Whitney test). The analysis of the dichotomic variables (response/no response) was made by means of a chi-squared test or a Fisher's exact test. Analyses were done by "intent to treat" on the entire treated population (all patients who received at least one dose of study medication). A logistic regression analysis was carried out using the SVR as the dependent variable. Univariated 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. Data were analyzed by STATA (StataCorp, 2005, Stata Statistical Software: Release 9.2. College Station, TX: Stata Corp.).

The sample size (164 patients; 82 in each arm of study) was calculated on the basis of a bilateral test of comparison of a proportion observed with respect to a theoretical proportion.[26] We aimed to detect differences above 20 percentage points if they existed (assuming a response rate of 40% in the best group versus 20% in the other group), with an alpha risk of 0.05 and a power of 80%.

Results

Patient Characteristics. Enrollment began in January 2003, and the trial was completed in October 2007. A total of 182 patients were included in this study (86 in the PEG 2b arm and 96 in the PEG 2a arm).

Patients who received at least one dose of medication were evaluated in the ITT analyses. Baseline characteristics, including histological findings in liver biopsies, were similar between the two treatment groups (Table 1). Most patients were male (73%). Mean overall age, weight, and height were 41 years, 68 kg, and 170 cm, respectively. Seventy-six percent of subjects had a history of illicit intravenous drug consumption. The mean time since their chronic hepatitis C infection was 18 years. The most frequent genotypes in our patients were 1 and 3 (45% and 34%, respectively). Baseline HCV-RNA concentration was higher than 600,000 IU/mL in 59% of patients and 400,000 IU/mL or less in 24% of patients.

Sixty-eight percent of patients had a fibrosis index of 2 or greater, and one third of our population had bridging fibrosis or cirrhosis in the liver biopsy. Thirty percent of the overall population had steatosis in the liver biopsy, with no significant differences among HCV genotypes, or antiretroviral treatment groups.

Mean time from HIV diagnosis was 11 years. Seventy-three percent of patients had a baseline HIV-RNA plasma level less than 200 copies/mL. The mean CD4+ cell count before initiation of HCV therapy was 598 cells/mm^3, and almost 92% of patients had basal CD4+ cell counts greater than 300 cells/mm^3. One hundred fifty-one patients (83%) included in this study received ART throughout the study period. Most of these patients (56%) were on a treatment regimen containing two nucleoside analog reverse transcriptase inhibitors plus one nonnucleoside analog reverse transcriptase inhibitor. Thirty-five patients (22%) had taken abacavir as a component in their ART regimen (16% and 28%, in the PEG 2b and the PEG 2a groups, respectively; $P = 0.084$).

Table 1. Baseline Characteristics of the Patients

Characteristic		Interferon			
		PEG 2b (n = 86)	PEG 2a (n = 96)	All (n = 182)	*P* Value
Male sex, n (%)		68 (79.1)	64 (66.7)	132 (72.5)	0.07
Age (years)*		40.7 (5.0)	40.6 (5.4)	40.7 (5.2)	0.9
Age at time to HCV infection (years)*		23.3 (6.9)	22.2 (6.6)	22.8 (6.8)	0.34
Baseline weight (kg)*		69.4 (12.3)	67.3 (10.8)	68.3 (11.5)	0.25
Baseline height (cm)*		171 (9)	170 (8)	170 (8)	0.68
HCV genotype, n (%)	1	32 (39.5)	47 (50.5)	79 (45.4)	0.53
	2	3 (3.7)	3 (3.2)	6 (3.4)	
	3	31 (38.3)	28(30.1)	59 (33.9)	
	4	15 (18.5)	15 (16.3)	30 (17.2)	
Baseline HCV-RNA >400.000 IU/mL, n (%)		65 (78.3)	69 (74.1)	134 (76.1)	0.60
Baseline HCV-RNA >600.000 IU/mL, n (%)		50 (60.2)	54 (58.1)	104 (59.1)	0.88
Baseline HCV-RNA >800.000 IU/mL, n (%)		48 (57.8)	50 (53.7)	98 (55.7)	0.66
Fibrosis score†	0-2	51 (70.8)	64 (71.1)	115 (70.9)	1
	3-4	21 (29.2)	26 (28.9)	47 (29.1)	
Baseline ALT (grade I- II), n (%)		63 (73.2)	73 (76)	136 (74.7)	0.73
HIV risk group, n (%)	IDU	69 (81.2)	68 (70.8)	137 (75.7)	0.18
	HMX	4 (4.7)	7 (7.3)	11 (6.1)	
	HTX	9 (10.6)	20 (20.8)	29 (16)	
	Others	3 (3.5)	1 (1)	4 (2.1)	
Baseline CD4 cell count (cell//mL)*		592.5 (269.2)	602.3 (279.6)	597.7 (274.0)	0.81
Baseline CD4 cell count >300 cell (mL), n (%)		78 (91.8)	88 (91.7)	166 (91.7)	1
HIV viral load < 200 copies/mL, n (%)		63 (74.1)	70 (72.9)	133 (73.5)	0.87

None of the differences was statistically significant. (Fisher's exact test for categorical factors and *t* test or Mann-Whitney *U* test for continuous).

*Mean (SD).

RBV, ribavirin; PEG 2b, Peg-interferon alfa 2b; PEG 2a, Peg-interferon alfa 2a; IDU, intravenous drug users; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Outcome. Response rates are summarized in Fig. 1 and Table 2. In the global intent-to-treat analyses, 44% of patients reached SVR (42% versus 46%, for PEG 2b and PEG 2a, respectively; $P = 0.654$). Among patients with HCV genotype 1 or 4, the rates of SVR were not different between treatment groups (28% versus 32%; $P = 0.676$). Likewise, no significant differences were found in SVR rates in patients with genotype 2 or 3 (62% and 71%; $P = 0.6$).

The proportion of patients who had HCV-RNA undetectable during therapy but relapsed in the follow-up was small in both treatment groups: 8% in the PEG 2b arm versus 6% in the PEG 2a arm ($P = 0.774$)

Fifty-two patients became negative for HCV-RNA after 4 weeks on PEG IFN therapy. Thus, an RVR was obtained in 35% of patients, and this response was similar in both treatment groups. There were no significant differences in RVR rates between arms of therapy within the genotype 1 or 4 group (21% in PEG 2b versus 16% in PEG 2a, $P = 0.587$), or the genotype 2 or 3 group (55% versus 78%, $P = 0.141$). The overall PPV of RVR for subsequent SVR was 81% (88% for PEG 2b versus 74% for PEG 2a, $P = 0.295$). Among patients with genotypes 1 or 4, the PPV was 75% (87% versus 62%, $P = 0.569$) and 82% for genotypes 2 or 3 (87% versus 78%, $P = 0.660$). The NPV of global RVR for not achieving SVR was 74% (79% versus 70% for PEG 2b and PEG 2a, respectively, $P = 0.360$). In the group of patients with genotype 1 or 4, the NPV was 78% (87% versus 72%, $P = 0.157$); whereas in those patients with genotypes 2 or 3 the NPV was 61% similar in both arms of therapy.

Of the entire population, an EVR was achieved in 115 patients (75%), and the rates were similar between treatment groups (69% versus 80%, $P = 0.133$). Regarding HCV genotypes, the rate of EVR in the genotype 1 or 4 group was 57% in PEG 2b and 71% in PEG 2a ($P = 0.181$); for genotype 2 or 3, the rate of EVR was 83% and 96%, respectively ($P = 0.197$). The overall PPV of the SVR for individuals showing an EVR was 64%, with almost identical PPVs between treatment groups. Likewise, we did not observe significant differences between treatments for genotypes 1 or 4 (50% versus 51%, $P = 1$) and genotypes 2 or 3 (76% versus 81%, $P = 0.743$). The NPV of not obtaining a SVR in patients who did not obtain an EVR was 100%, regardless of treatment and genotype.

Regarding baseline HCV-RNA, no differences in SVR were observed between the patients with low baseline levels (<400,000 IU/mL) or those with HCV-RNA 400,000 IU/mL or greater (55% versus 41%, $P = 0.154$). Moreover, the overall rate of SVR was independent of the degree of fibrosis ($P = 0.725$) and also in the analyses by treatment groups.

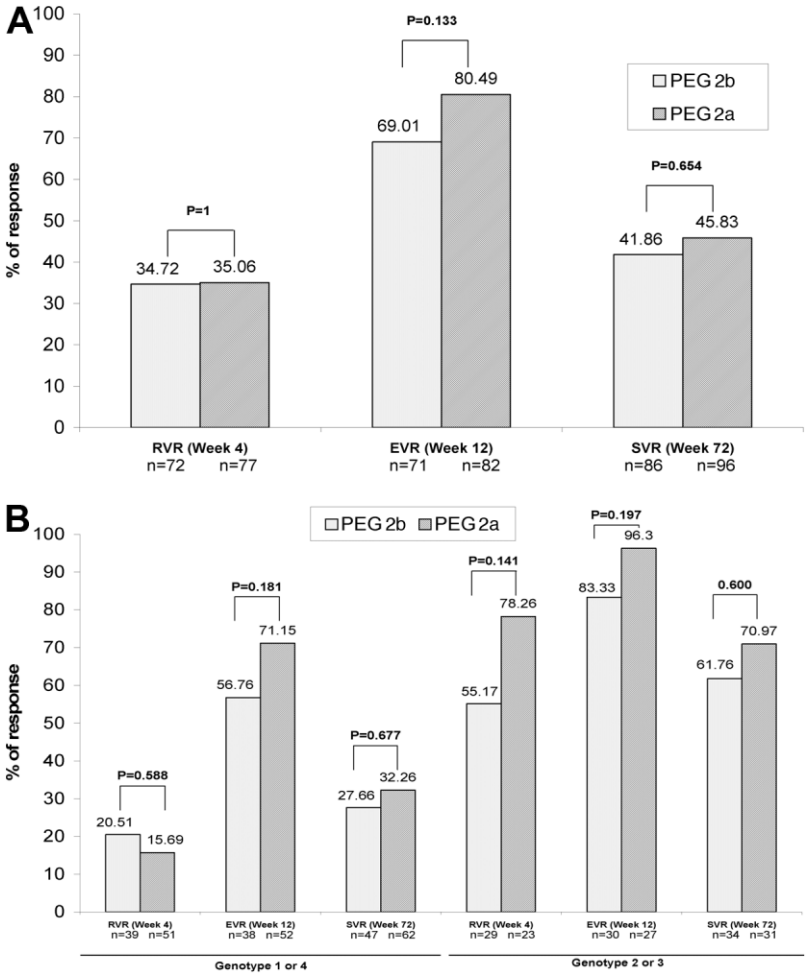

Fig. 1. Response rate by ITT. (A) Global; (B) By genotype. RVR, rapid virological response at week 4; EVR, early virological response at week 12; SVR, sustained virological response 24 weeks after cessation of therapy.

The overall sustained biochemical response rate seen in this study was 50%. Among patients with SVR, 14 (18%) did not achieve normal values of ALT at the end of follow-up.

To examine the influence of potentially important prognostic factors for SVR, we assessed the following variables by univariate and multivariate methods (Table 3): HCV genotype, baseline HCV-RNA and ALT concen-

Table 2. Percentages of Rapid Virological Response (RVR) and Early Virological Response (EVR) by Genotype and Their Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of SVR in the Overall Cohort and by HCV Genotype

	PEG 2b N = 86			PEG 2a N = 96			Overall N = 182			*P* Value*		
	1/4	2/3	All	1/4	2/3	All	1/4	2/3	All	1/4	2/3	All
RVR	21	55	35	16	78	35	18	65	35	0.587	0.141	1
PPV of SVR	87	87	88	62	78	74	75	82	81	0.569	0.660	0.295
NPV of SVR	87	61	79	72	60	70	78	61	74	0.157	1	0.360
EVR	57	83	69	71	96	80	65	89	75	0.181	0.197	0.133
PPV of SVR	50	76	65	51	81	64	51	78	64	1	0.743	1
NPV of SVR	100	100	100	100	100	100	100	100	100	1	1	1
SVR	28	62	42	32	71	46	30	66	44	0.676	0.600	0.654
SVR by degree of fibrosis												
0-1 (n = 51)	25	38	32	53	56	54	41	45	43	0.250	0.665	0.263
2-4 (n = 105)	34	73	48	27	75	43	30	74	45	0.598	1	0.701
SVR by baseline HCV-RNA												
≤400,000 IU/mL (n = 37)	37	37	37	55	80	67	47	61	54	0.649	1	0.117
>400,000 IU/mL (n = 132)	27	69	44	27	65	38	27	67	41	10.144	1	0.483

PEG 2b, Peg-interferon alfa 2b; PEG 2a, Peg-interferon alfa 2a.

Percentage sustained virological response (SVR) in overall patients, by genotype, degree of liver fibrosis, and baseline HCV viral load.

*Fisher's exact test: No statistically significant differences.

Table 3. Univariate and Multivariate Analysis of SVR Predictors

Effect	Odds Ratio	Lower 95% Confindence Limit OR	Upper 95% Confidence Limit OR	Pr Chi-Squared	Odds Ratio	Lower 95% Confidence Limit OR	Upper 95% Confidence Limit OR	Pr > Chi-Squared
PEG 2a versus PEG 2b	1.258	0.693	2.282	0.4501	1.606	0.813	3.171	0.1725
Therapy modifications (Yes versus No)	0.994	0.486	2.034	0.9872				
HCV RNA >800,000 IU/mL versus ≤800,000	0.797	0.438	1.451	0.4579				
HCV RNA >600,000 IU/mL versus ≤600,000	0.745	0.407	1.364	0.3406				
HCV RNA >400,000 IU/mL versus ≤400,000	0.575	0.286	1.156	0.1205				
Fibrosis 3–4 versus 0–2	1.051	0.541	2.040	0.8839				
Steatosis (Yes versus No)	1.116	0.400	3.110	0.8339				
ART (Yes versus No)	0.690	0.318	1.497	0.3473				
ABC use (Yes versus No)	1.059	0.495	2.263	0.8824				
Sex: male versus female	2.000	1.008	3.968	0.0475	2.828	1.241	6.447	0.0134
Age ≤ 40 years versus > 40 years	2.035	1.123	3.688	0.0192	2.637	1.308	5.317	0.0067
HIV Viral load ≤200 versus >200 cp/m	1.293	0.661	2.531	0.4531				
Baseline ALT	1.003	0.998	1.008	0.2501				
CD4 cell count ≤350 versus >350	0.453	0.199	1.032	0.056				
HCV Genotype: 2–3 versus 1–4	4.501	2.335	8.678	<.0001	4.618	2.317	9.202	<.0001
Weight > 75 kg versus ≤75 kg	0.680	0.334	1.385	0.2878				
EVR (yes versus no)	>999.999	<0.001	>999.999	0.9402				
RVR (yes versus no)	12.506	5.324	29.375	<.0001				
Age at the moment to be infected by HCV	0.973	0.929	1.020	0.3394				
Fibrosis 2–4 versus 0–1	0.767	0.385	1.525	0.4489				
CDC stage B versus A	0.610	0.248	1.502	0.1004				
CDC stage C versus A	0.452	0.210	0.975	0.1004				

For multivariate analysis only statistically significant values were included in the table. HIV, human immunodeficiency virus; ART, antiretroviral therapy; ABC, Abacavir; HCV, hepatitis C virus; ALT, alanine aminotransferase; PEG 2b, Peg-interferon alfa 2b; PEG 2a, Peg-interferon alfa 2a; RVR, rapid virological response; EVR, early virological response. Therapy modifications = any change in the initial doses of anti-HCV drugs that the patient needed during the study.

tration, degree of fibrosis and presence of steatosis in the liver biopsy before starting therapy, age at the moment of HCV infection, baseline CD4 cell count and plasma HIV viral load, HIV classification at baseline, use of ART for HIV, therapy containing abacavir, age, sex, baseline body weight, class of interferon, the need to modify the dose of HCV therapy, and on-treatment markers of good virological response (RVR and EVR). Male sex ($P = 0.047$), age 40 years or younger ($P = 0.019$), HCV genotypes 2 or 3 ($P < 0.0001$), and achieving an RVR ($P < 0.0001$) were significantly associated with a higher likelihood of SVR. When these variables and the class of interferon were included in the multivariate analysis, only genotype 2 or 3 ($P < 0.0001$), male gender ($P = 0.013$), and age 40 years or younger ($P = 0.007$) remained as independent predictors associated with better SVR rate.

Safety Evaluation. Eighty-one percent of the patients included in the study completed the 48 weeks of treatment; only 32 patients (18%) had premature discontinuation (14 in the PEG 2b and 18 in the PEG 2a group, $P = 0.7$). Nineteen (10%) patients discontinued treatment because of adverse events, 8% in the PEG 2b and 13% in the PEG 2a arms ($P = 0.467$). The main causes were as follows: five cases of psychiatric disorders, five cases of severe flu-like syndrome or general discomfort, four cases of thrombocytopenia or leukopenia, two cases of lactic acidosis, one case attributable to a severe debut of psoriatic arthritis, one case of severe weight loss with worsening lipoatrophy and one case of decompensated cirrhosis. Six patients in each therapy arm decided to withdraw therapy before 24 weeks, and one patient was discarded because of a protocol violation.

Ninety-six percent of our patients experienced some type of adverse effect (Fig. 2 and Table 4). The most frequently reported ones were general symptoms such as fatigue, anorexia, fever, myalgia, and headache (flu-like syndrome) that appeared in 87% of patients, especially at the beginning of treatment. Neuropsychiatric symptoms (irritability, apathy, insomnia, depression) were observed in 65% of patients. Hematological disorders were also frequent: anemia (hemoglobin <10.5 g/mL) was observed in 28% of patients early in the course of treatment (weeks 2-8), whereas leukopenia (<2500 cell/mL) and thrombocytopenia (<125,000 cell/mL) appeared in 42% and 38% of patients, respectively, throughout the first semester of treatment.

In general terms, the side effect profiles were similar in both groups of treatment. However, patients on PEG 2a

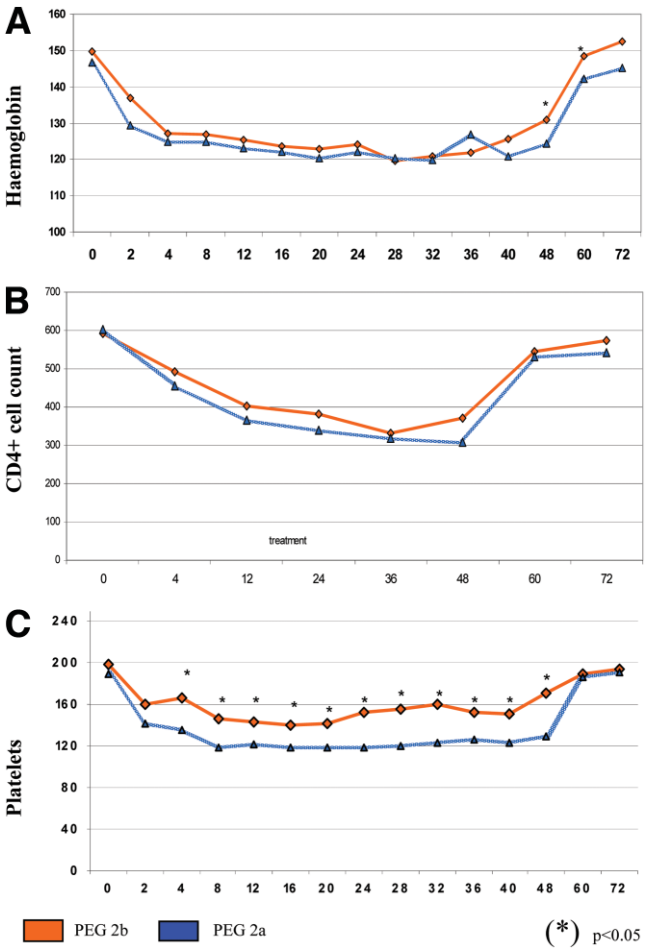

Fig. 2. Evolution of hematological parameters during the therapy: (A) mean hemoglobin; (B) mean CD4+ cell count; (C) mean platelet count.

showed a significantly higher incidence of leukopenia ($P = 0.004$) and thrombocytopenia ($P = 0.0037$) than patients on PEG 2b; also, patients on PEG 2b had a tendency to show more frequent events of flu-like syndrome ($P = 0.064$).

Almost half of the patients (49%) had a grade 3 adverse effect, with a significantly higher incidence in PEG 2a patients (57%) than in PEG 2b (40%) ($P = 0.018$). If we included those patients who stopped treatment because of pharmacological toxicity (grade 4 adverse effects), the incidence rate of severe adverse effects increased to 55% (46% on PEG 2b versus 62% on PEG 2a, $P = 0.037$)

Leukopenia was the most frequently reported hematological adverse event, with an overall prevalence of 42% (30% and 52% for PEG 2b and PEG 2a, respectively, $P = 0.0041$), and was mild to moderate in most cases. Of the patients that developed leukopenia, 19% needed dose drug reduction; 8 patients (2 in the PEG 2b and 6 in the PEG 2a group) required granulocyte-stimulating therapy and 3 patients discontinued treatment because of this adverse effect. Thrombocytopenia developed in 38% of patients (27% and 48% for PEG 2b and PEG 2a, respectively, $P = 0.0037$); 9% of patients had a platelet count decrease that required drug dose reduction, and two patients discontinued therapy because of thrombocytopenia. Anemia was present in 28% of patients, between both PEG therapy groups; in 9% of cases, the decrease in hemoglobin levels required a drug dose modification or erythropoietin administration (11 patients; five in the PEG 2b and six in the PEG 2a groups), but none of the patients discontinued the therapy for this reason. Seventy-five percent of patients who developed severe anemia, grade 3 or 4, were taking zidovudine in their scheme of ART.

One hundred eighteen patients in this study (65%) developed neuropsychiatric symptoms during therapy: irritability in 36%, depression (sadness, tiredness, apathy) in 32%, and insomnia in 26%, without statistical differences between both treatment arms. Twenty-two percent of patients required treatment with selective serotonin re-uptake inhibitors such as citalopram or paroxetine, resulting in a significant improvement in their symptoms. Five patients interrupted the interferon-based therapy because of this type of adverse effect.

During the treatment period, three patients developed thyroid dysfunction: two cases of hypothyroidism that needed substitution therapy with levothyroxine and one case of hyperthyroidism treated with metamizol. No patient stopped the HCV therapy for this reason.

Discussion

The cornerstone of treatment for chronic hepatitis C is the combination of pegylated interferon and ribavirin. Two pegylated interferon molecules are commercially available with this indication: PEG 2a and PEG 2b. Currently, several trials are focused on exploring new strategies that maximize treatment effectiveness using either PEG 2b or PEG 2a in different scenarios; nevertheless, to date, no data are available about head-to-head prospective comparative trials on efficacy in HIV-HCV co-infected patients. Therefore, our aim was to perform a controlled study to compare the efficacy and safety of these two therapeutic options in HIV-HCV co-infected patients.

In the current study, both treatment groups were comparable and presented similar baseline characteristics. It is important to emphasize that all patients received a dose of ribavirin adjusted to body weight.

The overall rate of SVR, the primary end-point of the study, was 44% and was similar for the two arms of PEG IFN therapy. The rates of SVR obtained within the different genotype groups (30% in patients with genotypes 1 or 4 and 66% in patients with genotypes 2 or 3) are good and similar to those reported in the most recently pub-

Table 4. Adverse Events: Frequency of Adverse Events During Treatment, Treatment Dose Reduction or Discontinuation Therapy

	PEG 2b (N = 86)	PEG 2a (N = 96)	Total (N = 182)	*P* Value*
Discontinuation				
Any reason	16	20	19	0.700
Adverse effect	8	13	10	0.567
Adverse Events:				
Any	95	97	96	0.708
Grade III	40	57	49	0.018
Grade IV	13	16	14	0.673
Grade III or IV	47	63	55	0.037
General symptoms:	91	**83**	**87**	**0.188**
Flu-like	71	57	64	0.064
Asthenia	71	72	71	1
Anorexia	49	40	44	0.233
Headache	22	14	18	0.172
Myalgia	22	13	17	0.114
Hematological findings				
Anemia	28	28	28	1
Neutropenia	30	52	42	0.004
Thrombocytopenia	27	48	38	0.004
Gastrointestinal symptoms	24	19	21	0.371
Neuropsychiatric symptoms	**69**	**61**	**65**	**0.352**
Depression	31	32	32	1
Irritability	43	30	36	0.089
Insomnia	22	29	26	0.311
Dermatological symptoms				
Hair thinning	16	11	14	0.392
Injection-site reaction	13	7	10	0.226
Mitochondrial toxicity	2	5	4	0.449

*Fisher's exact test.

lished trials in HIV patients.[14] The experience gained by medical professionals in managing these patients over recent years and the optimal use of anti-HCV drugs certainly has contributed to this increase in therapy effectiveness. In our study, the strong predictors of SVR resulting from the multivariate analyses were factors already known to be associated with a better response rate such as genotype 2 or 3,[8-10,13,27] age 40 years or younger, and male sex. Conversely, baseline HCV-RNA viral load and degree of liver of fibrosis were not related to therapeutic response in our series, probably because of the relatively small number of patients included in our study.

The tolerability of HCV therapy remains a weak point of these drugs; development of side effects proved to be very common in both groups of therapy, a finding that is in accordance with previously published studies.[8-10,13-15] More than half of our cohort required therapeutic intervention including dose modification or introduction of adjuvant therapy. In the current study, serious adverse effects (grades 3 and 4) were more frequently observed in the group of patients receiving PEG 2a.

The toxicological profile of the two PEG IFN molecules was similar, and comparable to those of previous studies. "General symptoms" such as flu-like, asthenia, and anorexia, were the most common adverse events observed in both treatment groups. Also, neuropsychiatric symptoms and hematological anomalies were very common. Hematological toxicity in the form of thrombocytopenia and leukopenia was observed more frequently in the PEG 2a arm; similar data were reported by other authors in HCV monoinfected[28] and co-infected patients.[29] Anemia showed similar rates of incidence in both treatment groups and was clearly associated with concomitant use of zidovudine; these data are in agreement with previously reported studies and confirm the importance of avoiding this therapeutic association.[29-31]

The dropout rate in our study was very low and was similar in both treatment groups. Close medical supervision of these patients and better management of side effects may have played an important role in this outcome. In addition, the rate of relapsers was low, and this may be related to the high doses of RBV administered to our patients, as suggested in one study with HCV-monoinfected patients.[32]

SVR is usually associated with ALT normalization.[33,34] However, in co-infected patients, the coexistence of other factors that can contribute to liver inflammation, such as alcohol, drugs, or antiretroviral therapy, may explain the high rate of patients (18%) with SVR that failed to

achieve sustained biochemical response in the current study.

About viral kinetics, it is noteworthy that the PPV obtained from the RVR for subsequent SVR was as high as 80% in our study, regardless of the type of PEG IFN therapy or the genotype group. Therefore, in accordance with other studies,[15,35-37] attaining RVR is highly predictive of attaining SVR. Conversely, failure to attain EVR was a consistent indicator of failure to achieve SVR (NPV 100%) in all cases.

We conclude that in HIV patients, treatment of chronic HCV with ribavirin combined with either PEG 2b or PEG 2a had no statistically significant differences in tolerance and efficacy.

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